ENGINEERING
MAN
FOR
SPACE

THE CYBORG STUDY

NASw-512

FINAL REPORT

GPO PRICE $ ____

OTS PRICE(S) $ ____

Hard copy (HC) $5.00

Microfiche (MF) $1.25

To N A S A (OART)
~~Biotechnology and~~
Human Research

Washington, D. C.
May 15, 1963

CORPORATE SYSTEMS CENTER
United Aircraft
FARMINGTON, CONNECTICUT

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TO

NASA (OART) Biotechnology and Human Research

Washington, D. C.

May 15, 1963

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ABSTRACT

A study has been conducted to gather data pertaining to limitations on man's adaptability to long-term space flights and to possible methods for considerably reducing life support problems during such flights. Specifically the applicability of artificial organs, drugs, and hypothermia during such flights in considered in detail.

In addition, there is included the study on the development of a mathematical and dynamic model of the human heart and cardiovascular system in a space environment.

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I. INTRODUCTION

The CYBORG study is the study of man. It concerns itself with the determination of man's capabilities and limitations under the unpredictable and often hostile conditions of space flight, and the theoretical possibility of incorporating artificial organs, drugs and/or hypothermia as integral parts of the life support systems in space craft design of the future as a means of reducing metabolic demands and the attendant life support requirements. By this approach it is hoped that the efficiency and longevity of the life process on board space flights may be increased. It covers these new areas in detail in order to determine whether their application or utilization can assure the continued contribution of man to the success of prolonged space flights or interplanetary exploration without threatening his safety during such flights. The idea of modifying man is an advanced concept which must supersede conventional thinking and which will, in the long run, provide us with basic research data in the fundamental physiology of man during the conditions of space travel.

The Phase I CYBORG study has two principal task areas. Task A is a detailed consideration of the advisability and practicability of using artificial organs, hypothermia and/or drugs in adapting man to a space environment.

Task B is the collection and study of data relating to the operation of the human heart in a space environment. This has included the development of a mathematical and physical dynamic model.

This report is divided into seven major sections. The sections on artificial organs, hypothermia, drugs, sensory deprivation, and cardiovascular models represent the detailed discussion of the roles each may play in space flights of the future.

Section II thoroughly analyzes the history, development, state-of-the-art, and future directions in the fields of the artificial lung, the artificial heart, the artificial kidney and extracorporeal pump oxygenating equipment. All of the problems associated with the development of such units, physical, mechanical, and physiological, are considered in detail. Various existing models of each of the units used in present-day clinical procedures are illustrated and evaluated. Conclusions based on this information indicate limited application of artificial organs to space craft life support system design, with certain reservations however.

Section III follows the same general plan of analysis with great stress being placed on the physiologic aberrations and responses to artificially reduced body temperature. Methods by which body temperature can be lowered either by external means or electrical neurologic stimulation are covered thoroughly. The effect of this temperature reduction on the major organ systems and their physiologic functions is carefully analyzed.

This work appears to indicate a potential role for hypothermia as a metabolic retarding element, both from the standpoint of space applications and terrestrial medical research contributions. The metabolic reducing effects of a hypothermic situation have been clearly demonstrated in many areas of clinical research. The ability, at some point in this research, to "suspend animation" by hypothermia becomes a significant possibility. In the preservation of red blood cells for instance, work under Navy Contract has already shown that the storage of the erythrocyte is possible for periods up to four years. Tagging and reinjection of these stored cells into living systems has indicated that their predetermined life cycle of approximately 120 days has remained unchanged by the lengthy period of hypothermic preservation.

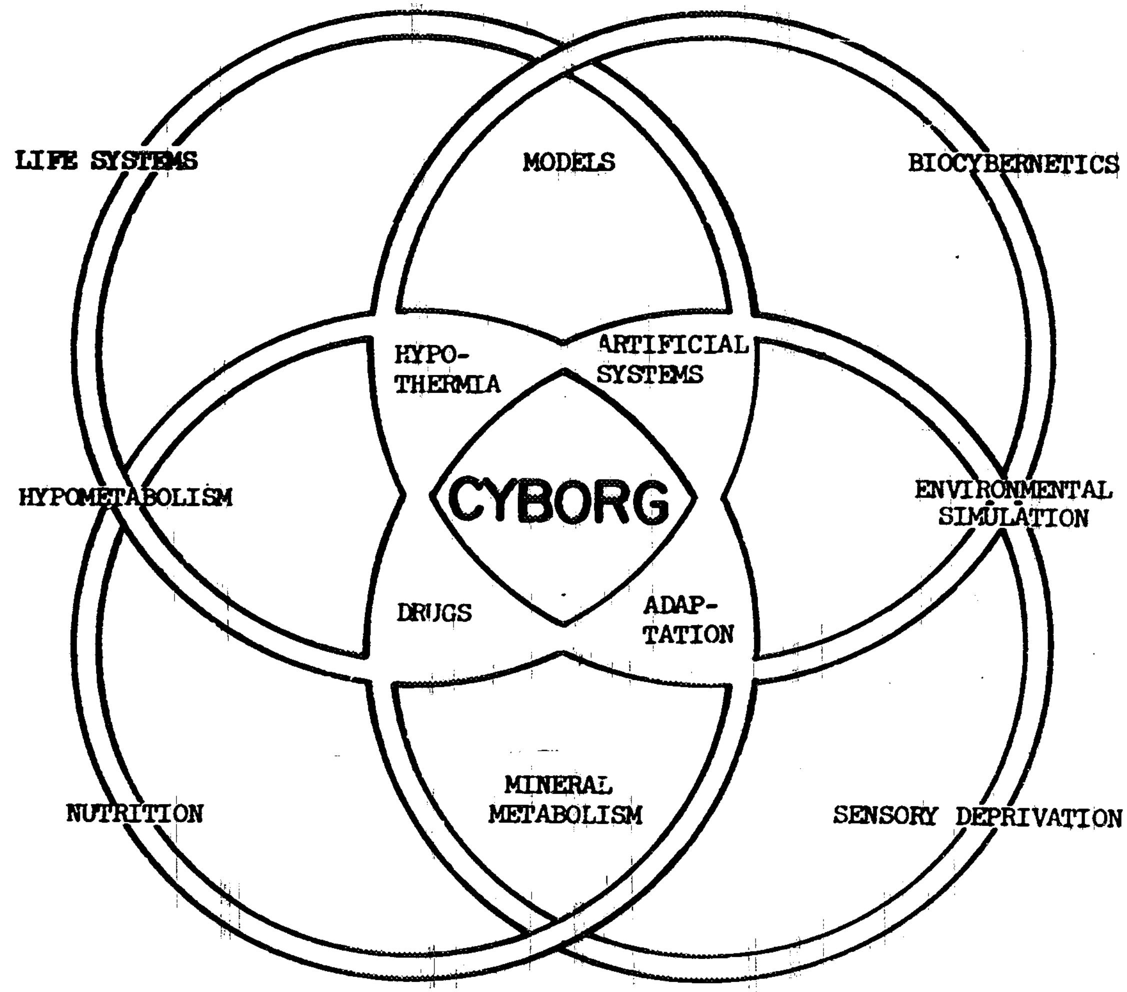
Section IV deals with a pharmacologic approach to the problems possibly to be encountered by space travelers. The use of drugs as adjuncts or protective agents in human physiology for space flight considerations is not new. Extensive work has been done on the radioprotective properties of a variety of chemical agents. The section on drugs in this report limits itself, however, to a study of those agents considered applicable only in the areas of anxiety, depression, fatigue, acceleration protection, thermoprotection, metabolism reduction, and motion sickness.

The use of chemical agents to alter physiologic function in space flights enables the operators to eliminate many variables in physiologic function and maintain precise and predictable control over these functions. However, although there is a great wealth of information on literally thousands of such agents, there is no central information source where the complete and varied effects of these agents, over and beyond those for which they were produced, may be obtained. It is felt that such an information source should be established immediately to fill this need. This agency would not only help the medical profession, but would also make its data available to those engaged in all forms of biomedical research.

The section on Sensory Deprivation (V) was heavily investigated because it is felt that this area can cause potentially debilitating effects on research pilots engaged in space exploration. It is considered a serious limitation on man's adaptability to space flights and, therefore, it has been emphasized in the CYBORG final report. In this area there has been extensive research and even the most preliminary analysis indicates that in hypodynamic situations where there is minimum sensory input, depending on the conditions, serious psychophysiologic deviations may occur in periods of less than one hour. This section discusses the aberrations resulting from exposure to hypodynamic conditions, identifies the environmental events associated with such effects and the sensory modality most susceptible to them, evaluates the characteristics of individuals most resistant or susceptible. In addition, it investigates methods of identifying and evaluating such characteristics and analyzes the hypodynamic aspects or possibilities of the space capsule and a space environment. It cannot be over-emphasized that the area of sensory deprivation must be actively pursued and that this area is worthy of continued, penetrating CYBORG research.

Section VI discusses the operation of the human heart in a space environment. Complete understanding of the multitude of complex interactions of organs and organ systems in the human will be a long time in coming. However, careful analysis of several of the more obvious characteristics of these systems has shown that their properties can, in many cases, be expressed in mathematical terms. The subsequent ability to duplicate and simulate any or all of these functions in terms of mathematical analogues will lead to an improvement in our understanding of the basic mechanisms and controls which affect the human system operation. By employing hypothetical, mathematical equivalents for computer simulation and high speed input variation analysis, we can begin to understand some of the complexities of human organ systems, their interface relationships, and, accordingly, be in a better position to predict function as influenced by new and changing environments.

Although the CYBORG study (NASw-512) has dealt specifically with hypothermia, drugs, artificial organs, and cardio-vascular models, we have expanded this concept to include other fields which cannot justifiably be reported in this document. However, it is felt that the area of calcium mobilization, a potentially severe limitation on man's physiologic adaptability to a space environment, should be investigated in detail. As was discussed in the interim CYBORG report presented to NASA-OART in January of this year, the calcium excretion levels evidenced by the three U. S. orbital man space flights were significantly elevated to arouse the interest of United Aircraft's Bio-Science group into an active pursuit of the reasons for this phenomenon. It has been proposed that mineral dynamics, along with mathematical and physical models of biological systems and sensory deprivation, be continued in subsequent phases of the CYBORG program.


LIFE SYSTEMS
MODELS
BIOCYBERNETICS
HYPO-
THERMIA
ARTIFICIAL
SYSTEMS
HYPOMETABOLISM
CYBORG
ENVIRONMENTAL
SIMULATION
DRUGS
ADAP-
TATION
NUTRITION
MINERAL
METABOLISM
SENSORY DEPRIVATION

II. ARTIFICIAL ORGANS

A. Introduction

The central theme of the section on artificial organs is the interrelationship between man and machine -- a special kind of machine which is coupled with man to aid his survival under adverse conditions, and so extend his range and type of performance. The resulting peculiar relationship develops a new man machine homeostasis which transcends the classic idea of the "milieu interieur" of Claude Bernard.

An artificial evolution accrues to man as a result of supplementing his organ systems. Since man has never been exposed to the environments of foreign planets we do not know whether he would evolve into some form which could exist under these conditions nor do we have the means on earth for fully investigating this phenomenon. Circumventing the slow process of natural selection by integrating man with machine makes possible the special man with increased functional capabilities. This is the Cyborg, the cybernetically controlled man who functions servomechanistically to cope with environments he does not fully comprehend.

In our study of the advisability and practicability of using artificial organs in adapting man to a space environment, we have entered into a detailed investigation into the artificial lung, heart, and kidney, and have studied methods of substituting these known artificial systems for a biological one.

In an effort to reduce the life support requirements during long term space flights, it must be appreciated that man's organs are not suited for space or are overdesigned in that they have large reserves which add weight and are not needed for flight. What follows in this section, then, is a thorough appraisal of the problems associated with the above mentioned artificial systems, a description in detail of the state of the art, and information pertinent to the possible incorporation of these systems as functional augmenting components in life support systems.

B. Artificial Lung

1. Physical and Chemical Aspects of Gas Exchange

Oxygen is carried by the blood both as a solute and as oxyhemoglobin within the erythrocytes. The quantity of oxygen which is dissolved in the plasma is normally about one-fiftieth of that bound by the hemoglobin, and will at normal barometric pressures be neglected in considering the oxygen-carrying capacity of blood.

The combination of hemoglobin and oxygen may be represented by the equation

$$Hb + O_2 = HbO_2 + Heat.$$

From this equation it is apparent that a high oxygen tension and a low temperature favor the formation of HbO_2. This equilibrium is also influenced by the pH. Hemoglobin is approximately 97 percent saturated at the partial pressure of oxygen in the air.

The erythrocyte equilibrates with great rapidity with the oxygen tension of the adjacent plasma. In the subsequent discussion it will therefore be assumed that the oxygen tension in the erythrocyte and in the plasma is the same.

The fundamental problem involved in the operation of blood oxygenators is the transfer of oxygen across a gas-blood interface. If blood and oxygen were exposed to one another without any turbulence within the liquid or gas, movement of the gas would depend solely on the kinetics of the individual gas molecules. This process is generally referred to as molecular diffusion. When the gas and liquid phases are subject to turbulence, the process is called eddy diffusion. Eddy diffusion, more rapid because distribution occurs through mixing, is the transfer mechanism of mechanical oxygenation. The situation is that of a gas phase and a liquid phase in contact at an interface. Each phase has associated with it a certain degree of turbulence. The partial pressure of the oxygen in the gas phase is P_G and that in the liquid phase is P_L. If No_2 equals the number of oxygen molecules which enter the plasma per unit time, then

$$No_2 = Ko_2A \quad (P_G - P_L)$$

where A is the area at the interface. The factor K increases with turbulence and temperature.

Several observations may be made about the preceding equation:

a. Turbulence

In order to explain the variation of K with turbulence, two films, one consisting of stagnant gas, the other of stagnant liquid, are postulated at the interface. The gas traverses these films by the relatively slow process of molecular diffusion, which is the rate-limiting factor in the oxygenation process. The greater the turbulence in each phase, the thinner these films become, with a consequent increase in the diffusion rate across the interface. Certain phases offer more resistance to eddy diffusion than others. It is of particular importance to provide turbulence to the high resistance phase. In blood oxygenators, the resistance of the blood phase is large compared to that of the gas phase, a phenomenon which is said to be due to the low solubility of oxygen in plasma. Producing turbulence in the blood results in a substantial increase in the speed of oxygenation, while turbulence in the gas phase has practically no effect. In the vertical cylinder oxygenator, a several-fold increase in oxygenation is noted when wire mesh screens are used instead of smooth metal plates. This may be attributed to the turbulence produced by the blood flowing down the uneven wire mesh surfaces.

b. Temperature

With increasing temperature, the factor K in the diffusion equation becomes larger, and this increases the rate of diffusion. On the other hand, at higher temperatures, oxyhemoglobin is more dissociated. This results in a greater value of P_L for any given saturation, with a consequent decrease in the rate of diffusion. In all perfusion systems, P_G is maintained at a value quite far above the value of P_L which is required for complete saturation. Under these conditions, the increase in K considerably outweighs the decrease in $P_G - P_L$, and the net result is an increase in the rate of oxygenation with increasing temperature. However, since the oxygen requirements of the perfused subject also vary with his temperature, it is questionable whether the subject's oxygen debt is reduced by oxygenating the blood at, say, 37°C instead of 30°C.

c. Oxygen Tensions

The equation shows that the rate of diffusion is proportional to the difference in oxygen tensions between the gas and liquid phases. The value P_G is directly proportional to the absolute pressure of the ventilating gas. Thus, operating the oxygenator above atmospheric pressure increases the rate of diffusion. If the blood becomes saturated with oxygen under these conditions, some of the dissolved gas may be expected to come out of solution when the blood is returned to atmospheric pressure. Whether a limited amount of minute oxygen bubbles would be injurious is uncertain. On the other hand, operating the oxygenator below atmospheric pressure allows simplification of the extracorporeal circuit. Because in this case the oxygenator may draw its own blood, the pumps that carry the blood from the veins and from the coronary sinus of the heart may be dispensed with. The decrease in rate of oxygen diffusion is compensated by the reduced blood holdup resulting from the elimination of two pumps.

2. Carbon Dioxide Elimination

It is desirable, although it does not appear to be essential in short-term perfusions, to maintain a constant pH in the blood by eliminating CO_2 at an appropriate rate. The equation which describes CO_2 elimination is

$$NCO_2 = KCO_2A\ (P'_G)$$

where P' represents the partial pressure of CO_2, and KCO_2 is the proportionality constant. From data for the diffusion of O_2 and CO_2 through water, KCO_2 is estimated to be approximately 25 times KO_2. This explains why elimination of CO_2 may be readily achieved in spite of the fact that the diffusion gradient can never exceed the plasma CO_2 tension (normally 40 mm Hg). In film oxygenators, CO_2 elimination usually surpasses formation unless P'_G is maintained between 1 percent and 3 percent in the ventilating gas. In the bubble and foam oxygenators, however, the gas flow may be limited by the capacity of the defoaming system.

3. Oxygen Requirements

When bypassing the heart and lungs of the average adult person, approximately 5 ml of oxygen per minute into every 100 ml of blood passing through the extracorporeal circuit is needed. A slightly smaller quantity of carbon dioxide must also be eliminated at the same time. Blood flow rates through the circuit of 3 or 4 liters per minute require the introduction of 150 to 200 ml of oxygen per minute and the removal of a nearly equal quantity of carbon dioxide. Every 100 ml of blood contains about 15 gm of hemoglobin and every gram of hemoglobin is capable of combining with 1.34 ml of oxygen. Thus approximately 20 ml of oxygen can be carried in the form of oxyhemoglobin by every 100 ml of blood, whereas the amount of oxygen held in physical solution in the plasma amounts to only 0.3 ml per 100 ml of blood. The reaction between hemoglobin and oxygen is practically instantaneous. The problem of simulating normal gas exchange then resolves itself into that of maintaining appropriate tensions of these gases in the immediate neighborhood of the hemoglobin containing erythrocytes.

In the human lung, the tension of the gases in the alveolus is approximately as follows (expressed as millimeters of mercury) 570-nitrogen, 103-oxygen, 40-carbon dioxide, and 47 water vapor. The blood in its brief passage through the pulmonary capillaries, approximately one-eight of a second, comes into equilibrium with the tension of these gases in the air sac. Equilibrium is reached in this very brief period despite the fact that there are interposed between the blood and the gas mixture two biological membranes, one the wall of the blood capillary, and the other the wall of the gas-containing alveolus.

4. Dimensions of Blood-Gas Interface

The surface area of the lining of the pulmonary capillaries in an adult human lung has been estimated as approximately 100 square meters. However, it is not necessary in an artificial lung to provide a blood-gas interface of such a large area or to create a film no thicker than the radius of a pulmonary capillary. Without exceeding the normal barometric pressure, the tensions of the gas mixtures exposed to the blood can be varied by eliminating the nitrogen and increasing the tension of the oxygen almost sevenfold, so that the area of the fluid gas interface might be considerably reduced or the thickness of the blood film increased without retarding attainment of equal tensions of oxygen in the plasma and ambient gas. Similarly prolonging the time of exposure of the blood film to the gas mixture allows the gas exchange to occur with a smaller area and thicker film. It is also obvious that equilibrium could be reached more rapidly if the dual membrane between the fluid and the gas which exists in the biological lung could be eliminated in the artificial lung.

These considerations were quickly seized upon by investigators attempting to accomplish the normal gas exchange of the blood by artificial means. In the extracorporeal blood circuits currently employed in operations on human patients, a free blood-gas interface is used and the blood is exposed to tensions of oxygen in excess of those in the alveoli. Despite the inevitable retardation of gas exchange, investigative work is currently being carried on to develop an artificial lung in which an extremely thin plastic membrane is interposed between the blood and the gas.

5. Film on Vertical Smooth Surface

To accomplish a satisfactory exchange of gases between the plasma and the ambient gas mixture with anything like the speed and efficiency which are necessary, the stream flow in the tubing of the extracorporeal blood circuit must be changed to a large, thin film of blood in contact with the appropriate gas mixture.

Blood can be filmed on the inner surface of a vertical revolving cylinder. Revolution of the cylinder is necessary to maintain the blood film by centrifugal force. With the cylinder stationary, the blood descends in rivulets. The blood is introduced at the top of the cylinder in a fan-shaped horizontal jet in the direction of revolution and tangential to the cylinder. The blood then descends in a thin film on the inner surface of the cylinder and is collected in a stationary cup which closely surrounds the knifelike edge of the bottom of the vertical revolving cylinder. Blood is let from this stationary cup in a stream flow through tubing and pumped back into the subject's arterial system. As mentioned earlier, it is highly desirable that the volume of blood contained in the extracorporeal circuit remain constant at all rates of blood flow through it. In most oxygenators of the film type, if the venous blood is passed directly through the oxygenator and then pumped directly back to the subject, the thickness of the film will be directly proportional to the rate of blood flow. Under these circumstances, if the blood flow is increased during the operation of the extracorporeal circuit, a greater amount of blood will be held in the artificial lung, thus depleting the subject's circulating blood volume. If blood is added to the circuit to compensate for this, it becomes necessary to withdraw blood from the circuit as the blood flow is diminished in order to avoid hypervolemia in the subject.

This problem has been very simply solved by maintaining a constant flow of blood through the artificial lung despite varying rates of blood flow through the extracorporeal circuit. In one model of the screen-type oxygenator, this is accomplished in the following manner (Fig. II-1). The maximum flow rate through the circuit during cardiopulmonary bypass is estimated from the weight or surface area of the patient. The blood from the vena cava is led

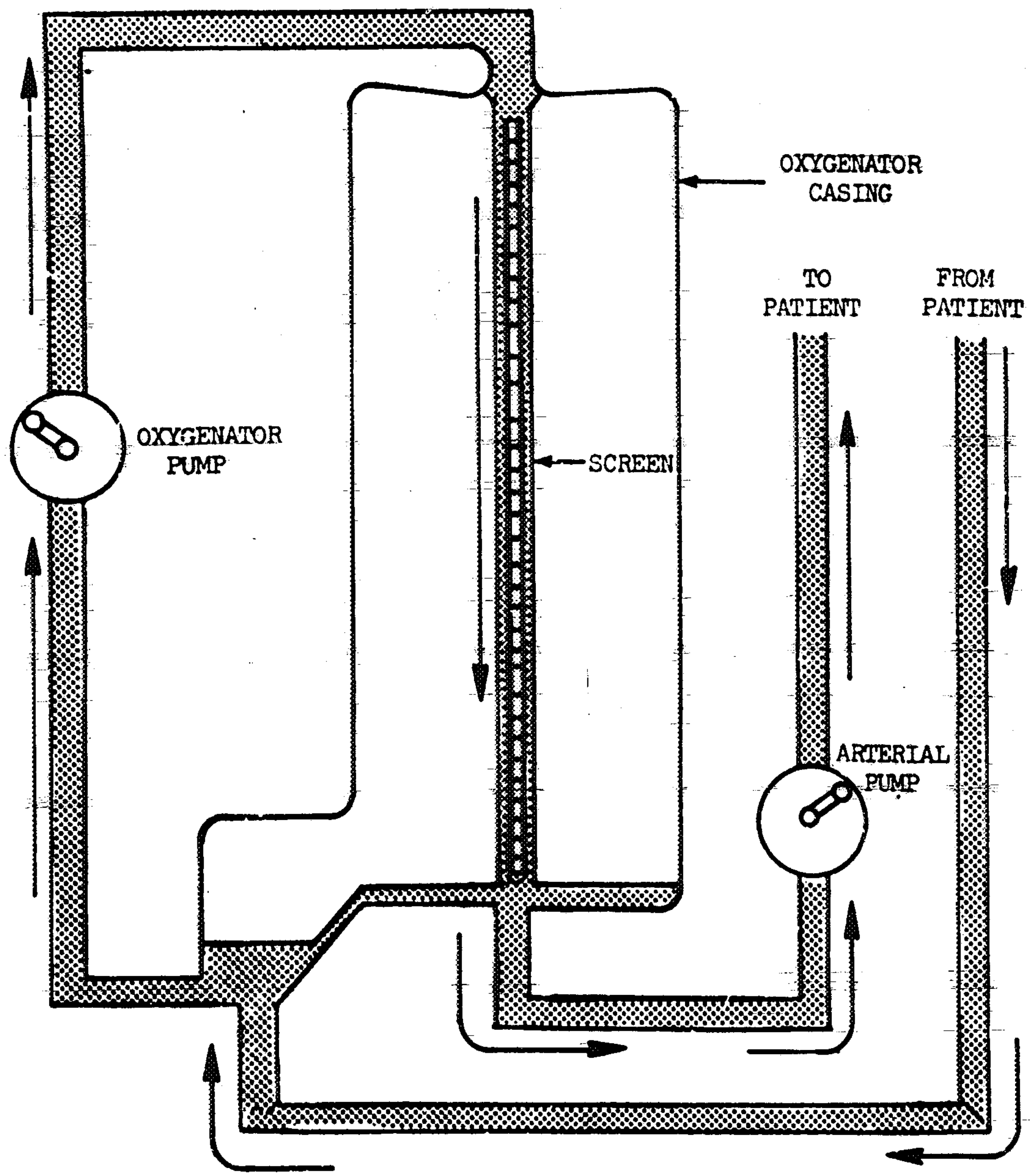


Fig. II-1 Diagram of Vertical, Screen Pump Oxygenator Illustrating Circuit to Maintain Constant Blood Volume at Variable Flow Rates by gravity into a reservoir at the bottom of the oxygenator case. This reservoir also receives blood overflowing from a higher reservoir immediately beneath the screens of the oxygenator. From this lower reservoir with its admixture of oxygenated and unoxygenated blood, the blood is pumped into the distributing head of the artificial lung at a constant rate which is greater than the maximum estimated venous return of the patient. Oxygenated blood is returned to the subject's arterial system from the upper reservoir. The rate of pumping the oxygenated blood back to the subject is automatically controlled by a level-sensing device in the lower blood reservoir. When the level in the lower reservoir tends to rise because of a greater flow from the vena cava, the pump returning oxygenated blood to the patient from the upper reservoir is immediately accelerated. Conversely, a diminishing flow from the vena cava will tend to make the level in the lower reservoir fall, which automatically results in a slower action of the pump returning oxygenated blood. The electronic device is sensitive enough to maintain the volume of blood in the extracorporeal circuit constant within 25 or 30 ml at widely varying rates of blood flow. The maintenance of both a constant thickness of the blood film on the screens and a constant level of blood in the reservoir at the bottom of the oxygenator accomplishes the desired result of an unvarying volume of blood in the circuit at all rates of flow.

6. Film on Rotating Disks

A second method of performing gas exchange in the extracorporeal blood circuit is accomplished by establishing a blood film upon the peripheral portion of vertical plates or disks revolving about a horizontal axis. The disks dip into a reservoir of blood in a trough below the revolving axis. With every revolution of the disks, the film of blood exposed to the ambient gas mixture is wiped off and a new blood film established and exposed to oxygen. This is an interesting method of constantly and rapidly renewing the film of blood exposed to the gas. The capacity of this artificial lung to accomplish the gas exchange can be increased by increasing the diameter or number of the disks. The two chief objections to this type of artificial lung are that the volume of blood held in the apparatus is relatively large compared with its ability to accomplish the gas exchange, and secondly, that there is a tendency to frothing at higher rates of revolution of the disks and a tendency for a solid film of blood to be established between disks which are very close together. The disks are mounted close to one another in order to increase the efficiency of the oxygenator by producing a large film area relative to the volume of blood held in the trough. The revolution of the axle is made as rapid as possible without producing foam in order to renew the blood film as frequently as possible, thus increasing the efficiency of the apparatus. An illustration of this spinning disc oxygenator is shown in Figure II-2.

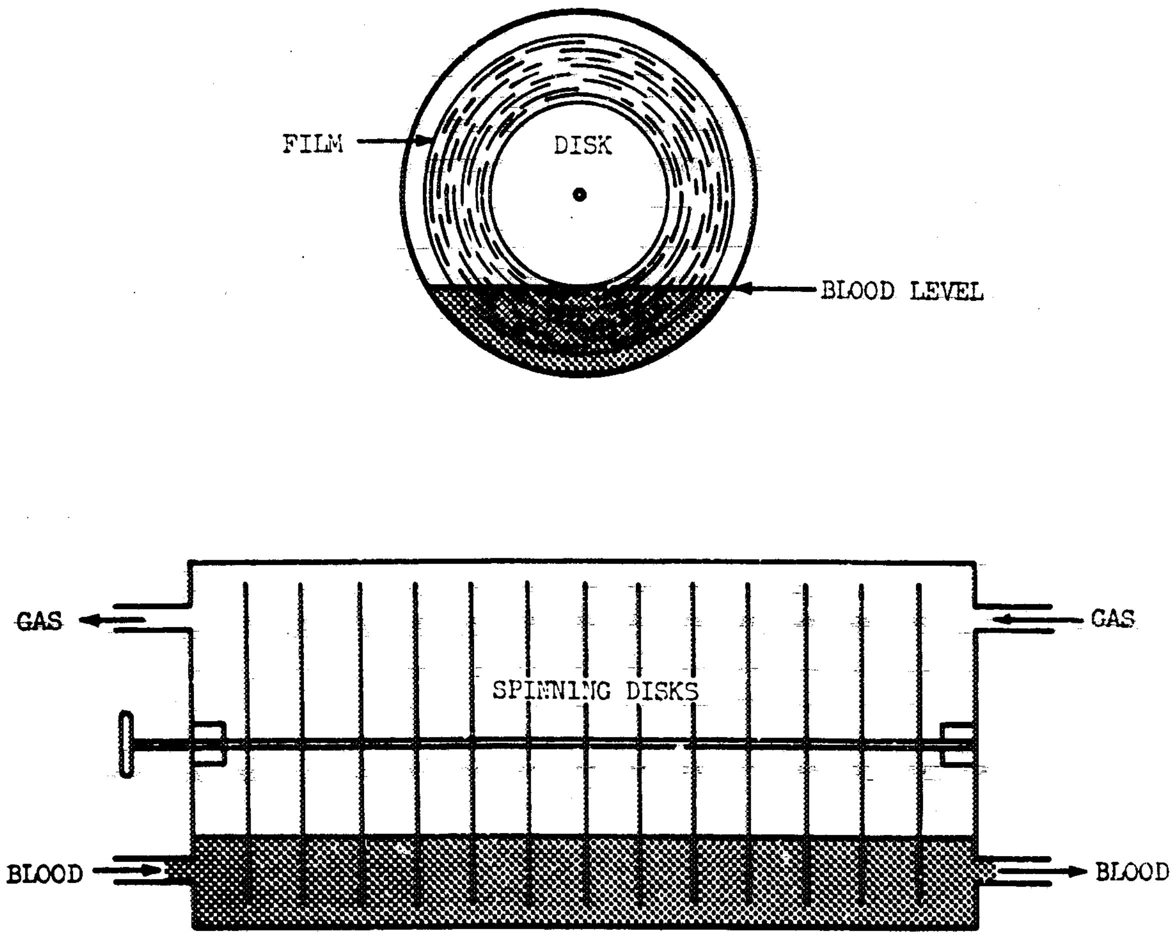


Fig. II-2 Spinning Disc Oxygenator: Schema

7. Film on Vertical Wire Screens

Wire screens are the most efficient turbulence-producing surface. Blood flowing by gravity over a wire screen travels rapidly in a very thin film across the meshes of a screen, tends to heap up on the upper surfaces of the horizontal wires, and then descends again in a thin film across the mesh below. Thus there is thorough mixing of all the elements of the blood from this mild turbulence which does not result in foaming. Obviously, if the meshes of the screen were too large, or the blood flow over the screens too small, the blood film across the mesh would not be established, or could not be maintained. An example is the Stedman packing oxygenator. Stedman packing is a tower packing used by the chemical industry in processes requiring intimate contact between liquids and gases. It consists of stacks of stainless steel wire cloth disks. Each wire disk is embossed and perforated so that it presents a pattern of pyramids, valleys, and holes. Blood is distributed at the top of the column and flows downward in a continuous stream from disk to disk. The oxygen is delivered at the bottom of the column just above the blood pool that runs off the column. A tight fit between the disks and the casing assures that the oxygen passes upward through the disks. A diagram of this oxygenator is shown in Figure II-3.

The oxygenator does not foam since there are no moving parts and the oxygen moves past the blood rather than through it. If the sheets are not wet the filming of the blood is imperfect because of channeling. Since the sheets are spot-welded together it is possible to inspect only the exterior surfaces, and it is necessary to rely on strong alkaline solutions for cleanliness. Obviously, the number of screens or their width should be varied according to the volume flow per minute over them in order to maintain the most efficient film thickness. Screen oxygenators of the type described are currently being used in operations on human patients.

8. Film on Bubbles of Oxygen

Still another method of accomplishing the gas exchange is by the production of oxygen bubbles in the blood passing through the circuit. A diagram is presented in Figure II-4.

Three distinct gas-liquid phases are apparent when the oxygenator is in operation. (1) At the bottom there is a pool of blood through which bubbles are rising freely as they are emitted from the oxygen manifold. In order to prevent oxygen embolism, the bubbles must have a rate of ascent greater than the rate of descent of the blood being withdrawn from the oxygenator. The larger the bubble, the more rapidly it climbs. At low oxygen flows, the bubble size is determined largely by the size of the orifice; the diameter of the bubble is proportional to the cube root of the diameter of the needle. (Bubbles released from coarse sintered glass disks are not consistently large enough to avoid gas embolism under normal operating conditions.) (2) Above the blood pool there is a foam column where the bubbles are separated by rather heavy blood films. (3) The bubbles above the blood distributor are bound by thin blood films since only the blood released by the defoaming baffle passes down through them.

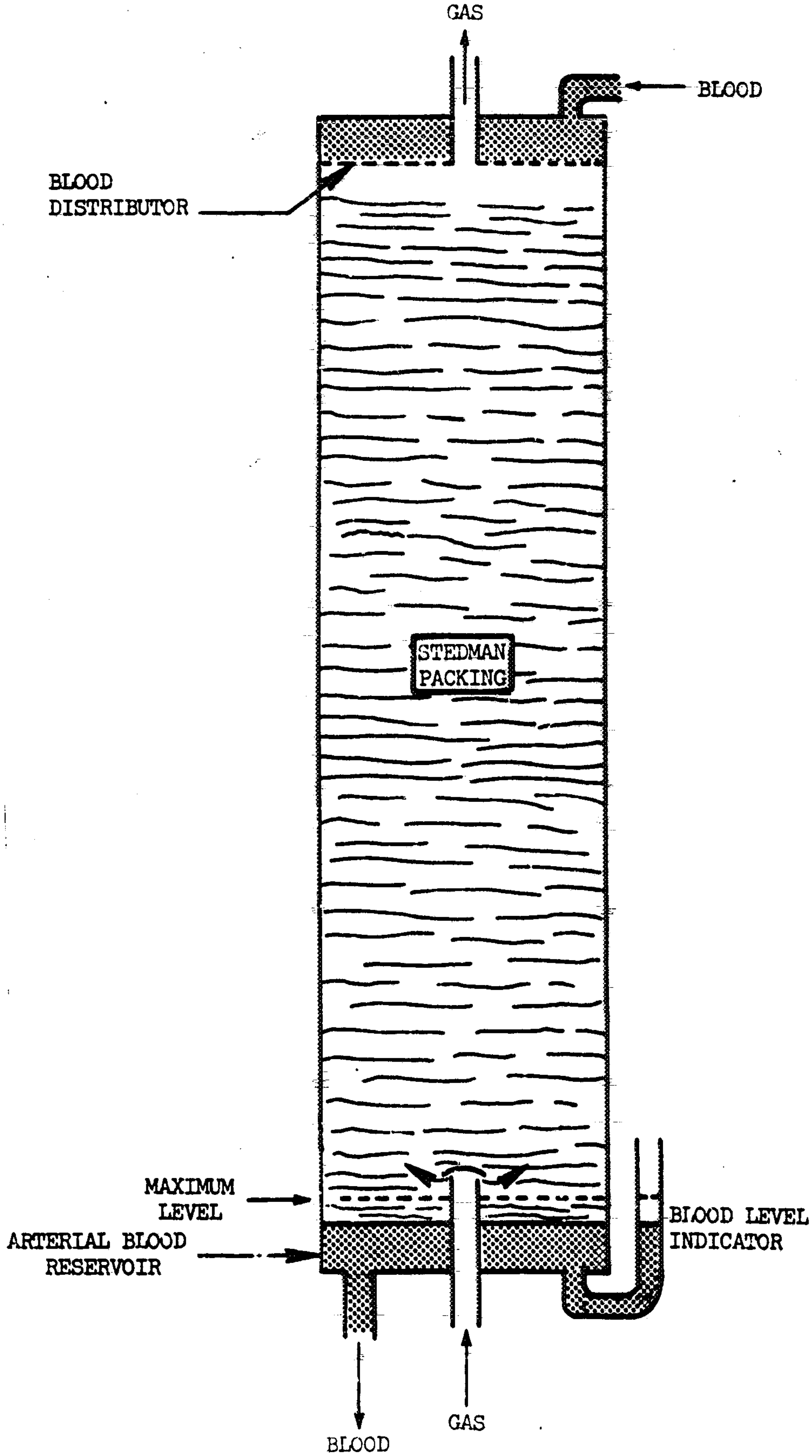


Fig. II-3 Stedman Packing Oxygenator: Schema

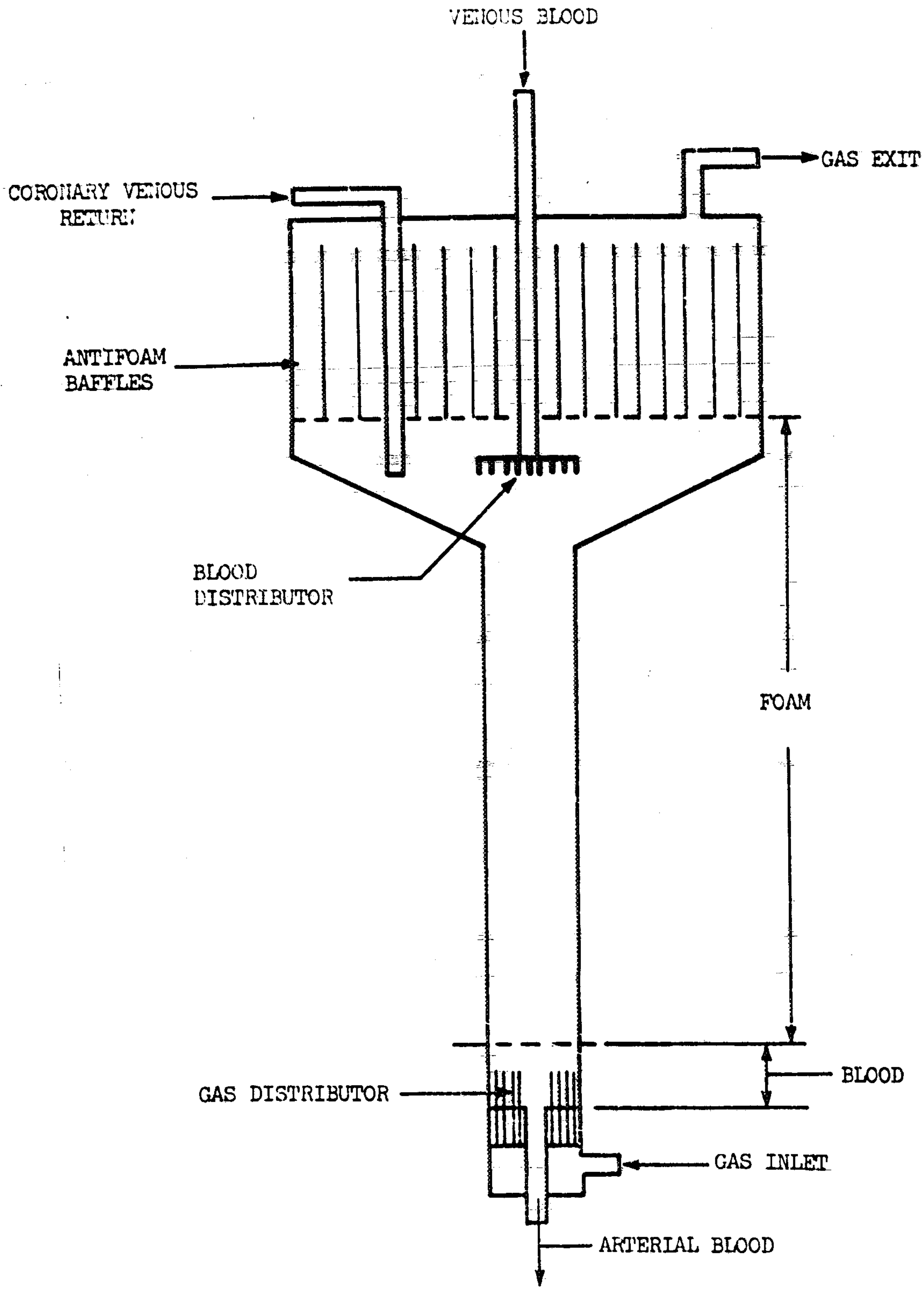


Fig. II-4 Foam Oxygenator: Schema

The widespread clinical use of this type of oxygenator has resulted in the early discovery and study of certain undesirable features of this method of accomplishing the gas exchange. The sphere is the least efficient geometric form in which to produce the greatest blood-gas interface per volume of gas or blood. It is apparent that the smaller the bubble, the more efficient is the gas exchange. It is of the utmost importance to eliminate all bubbles, even of the microscopic size, before the blood is returned to the systemic arteries of the subject. Attempts to accomplish this have taken a variety of forms: mechanical rupture of the bubble, passage of the mixed blood and oxygen over shredded plastic material coated with antifoam agents, etc. None of these methods has been wholly satisfactory. Antifoam agents are lethal in small amounts when in solution in the blood. Microscopic emboli of oxygen, despite all precautions, may occur. Similarly, small fibrin emboli, despite the use of heparin, may form in the presence of the marked foaming. Instances of central nervous system damage have occurred not infrequently from the use of this type of oxygenator. A reservoir of blood between the oxygenator and the arterial blood pump is necessary to permit oxygen and fibrin emboli to rise to the surface. The blood at the bottom of the reservoir is returned to the patient. Even if such a reservoir is completely effective, it has the undesirable feature of increasing the blood volume in the extracorporeal circuit.

Adequate elimination of carbon dioxide with the bubble-type oxygenator is difficult, if not impossible. Because of excessive foaming, it is not possible to pass sufficient oxygen through the blood to maintain a normal carbon dioxide tension. However, the respiratory acidosis tends to be self-limited as the higher the carbon dioxide tension in the blood, the greater the graduation in pressure between the blood and the gas, so that equilibrium is finally reached at a tension of carbon dioxide considerably higher than normal. A final disadvantage to the use of these oxygenators is that it is not possible to maintain a constant volume of blood in the circuit at varying rates of blood flow.

In clinical practice and in animal experiments, it has been found that the smaller the blood flow and the shorter the period of bypass of the heart and lungs, the greater is the chance of survival of the patient or animal. Proponents of bubble-type oxygenators have, therefore, advocated blood flow rates in patients in the neighborhood of 25 to 40 ml per kilogram of body weight. Surgeons using these oxygenators attempt to complete the open cardiac phase of the operation within 10 or 15 minutes, because the chances of survival diminish rapidly therafter. This is in contrast to the experience in animals and man using a screen-type oxygenator in which the entire cardiorespiratory functions have been taken over successfully by the extracorporeal circuit for periods between 1 and 2 hours with prolonged healthy survival. Furthermore, the flow rates in the screen-type oxygenators are always kept as large as possible, and roughly average 70 ml per kilogram body weight per minute in adults, and higher in children.

9. Gas Exchange through Membrane

It is apparent that all danger of gas embolism could be eliminated if the extracorporeal blood circuit were completely closed and the gas exchange took place through an extremely thin plastic membrane simulating the capillary and alveolar walls of mammalian lungs. The engineering difficulties in the construction of such a closed circuit are obviously great, but currently work is being carried out on this project in a number of places. In these membrane oxygenators, a very thin film of plastic sheeting is interposed between the blood and an atmosphere of oxygen. Wire screen between the plastic sheets which enclose the blood permits the circulation of oxygen. These oxygenators have been constructed in two main forms. In one, the polyethylene bags separated by wire screen are coiled into the form of a cylinder. In the other, the polyethylene bags and screens are arranged horizontally in the form of a large, multilayered sandwich. Originally, films of polyethylene 0.001 inch in thickness were used. It has been subsequently found that Teflon 0.0005 inch in thickness will transmit 3.2 times as much oxygen as a polyethylene film 0.0008 inch in thickness.

Membrane oxygenators of this type are now being studied on experimental animals and have been successfully used in human patients. In addition to eliminating the hazard of gas emboli, the closed blood circuit of membrane oxygenators should result in a diminution of the amount of heparin required to keep the blood incoagulable, as nonwettable plastic surfaces are used throughout. The elimination of carbon dioxide with the maintenance of a normal or slightly reduced carbon dioxide tension in the blood leaving the oxygenator can again easily be accomplished by regulating the rate of flow of the gas mixture between the layers of the plastic bag sandwich. Whether membrane oxygenators will eventually prove to be safer and as efficient as artificial lungs with a free gas-fluid interface remains to be seen. Certainly they offer a number of theoretical advantages over the screen type or rotating disks, but much work remains to be done to perfect them.

The original successful membrane lung of Clowes as well as modified designs have been described in current literature. In all these devices, blood flows as a thin film bounded above and below by porous membranes. O_2, maintained outside the membranes, diffuses across them and into the blood; CO_2 diffuses outward and escapes. Schematic drawings of the Clowes lung and a Pierce modification are shown in Figures II-5 and II-6.

10. Development of the Oxygenator

The blood oxygenators have been primarily developed because of a need for oxygenating the blood during temporary by-pass of the heart when performing heart surgery. The oxygenator type used widely is the bubble variety but the disc design is now gaining wider acceptance because of less difficulty in its operation and better results. The membrane oxygenator is being improved and will most probably ultimately be the type most frequently used because theoretically and practically it will most closely approach the

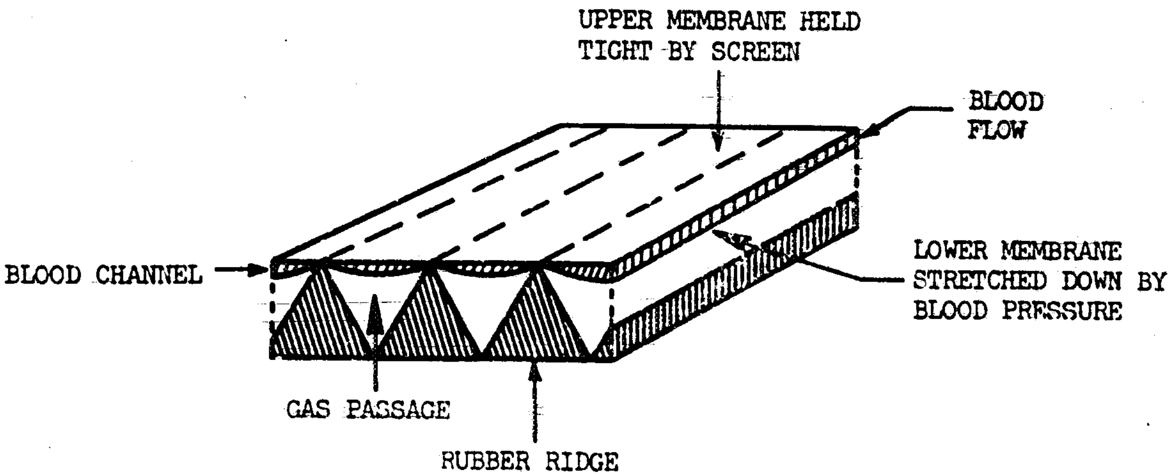


Fig. II-5 Schematic Representation of Blood Channels in Clowes Membrane Lung

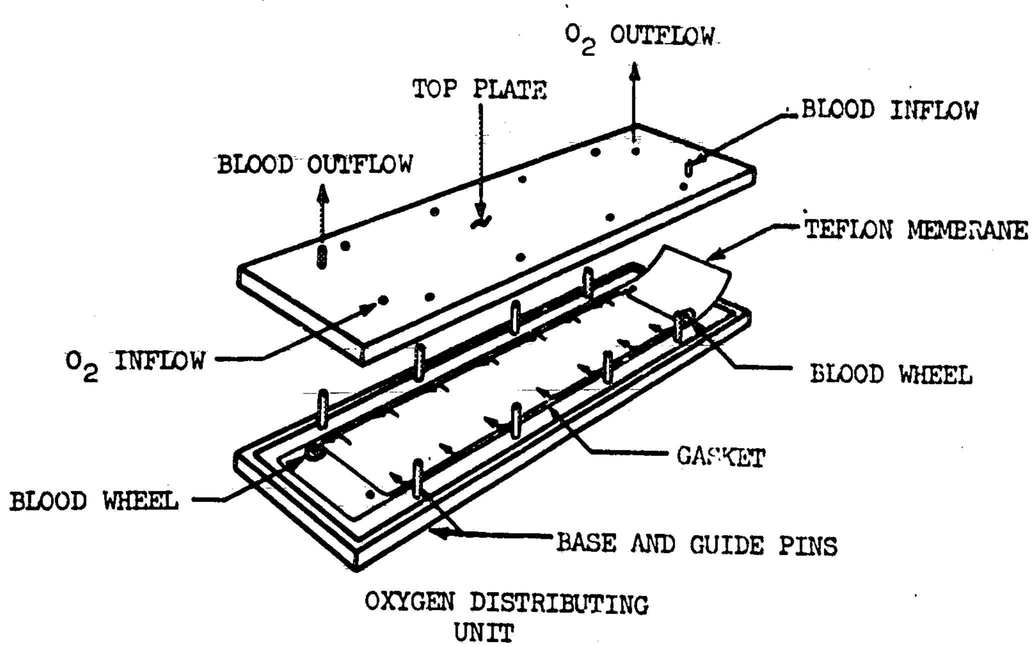


Fig. II-6 Basic Unit of Peirce Modified Membrane Lung function of the lung and can be engineered into a compact portable model. Table II-1 gives a comprehensive picture of the principal oxygenator systems.

With the advent of instrumentation to successfully oxygenate blood with minimal injury in a purely clinical situation, it has been possible to free man from dependence on his lungs for the introduction of oxygen and carbon dioxide removal. It will, no doubt, be possible to construct oxygenators of the membrane type which would be compact and portable enough to allow the incorporation of a respiratory module as a backpack or a capsule component to relieve man of his respiratory needs during space probes or in alien environments.

The problems inherent in the present state of the art make the use of extracorporeal components for augmenting man's respiration in the immediate future unless actively pursued experimentally.

C. Extracorporeal Circulation Pumping

1. Introduction

The use of artificial devices in the cardiovascular system, either extracorporeal or intracorporeal, to maintain adequate perfusion, presents an intriguing but complex concept. A thorough study was made of existing experimental extra- and intracorporeal circulatory devices, the details of which are included in this section.

The problem of extracorporeal circulation with a heart-lung machine has been the object of intense research for almost 20 years. The first few successful results in man were reported in 1953 and 1954. Gibbon in 1953 used this technique in operation on a 17-year-old boy for an atrial septal defect.

Andreassen & Watson (1953) published a detailed physiologic analysis of their experiments with the use of cross circulation as a method for cardiac by-pass. Warden et al (1954) made a thorough experimental investigation of the problem. In the same year this technique was introduced by Lillehei and co-workers, with brilliant results. In 1955 they started their series of direct-vision intracardiac surgery by means of controlled cross circulation.

The pumps which have been employed are of the reciprocating or constant-injection type. In the reciprocating type two automatically acting internal valves are required, one on the intake side of the pump, and the other on the output side. Internal valves in the blood circuit are undesirable for a number of reasons. They increase the difficulty of cleaning the apparatus, they may cause hemolysis, and they produce unnecessary turbulence which may result in the deposition of fibrin and platelets. Internal valves may be eliminated in intermittent pumps by an external device which occludes an

OPERATION AND CAPABILITY OF VARIOUS OXYGENATORS

	Principle	Authors	Max. O_2 Uptake, ml/min.	Volume Capacity ml	Interchange Area Sq.m.	Hemolysis, Plasma Hb mg.%/hr.	Advantages	Disadvantages
Natural human	Membrane diff.	--	3000	600-800	80-100	--	--	--
Ideal	Membrane	--	500	1000	--	none	--	--
	Stationary Screen	Gibbon-Mayo	150-200	2500	5	30-80	tested; calm blood flow	recirculation
	- do -	Mark Corp. Munich-Berlin	150-200	3000	4-5	40-100	- do -	- do -
	Revolving:	Crafoord-Senning Brom, Geissen	160-200	2500	3 x 5 rpm = 15[illegible]/min.	40-60	large area; cyl. used only once	turbulent blood flow
	a) cylinders	Kay-Gross	200	2000	1 x 110 rpm = 110/min.	20-140	large area;	- do -
	b) discs	Dennis	150	1000	1.6 x 24 rmp = 40/min.	40-80	easy cleaning, quick set-up	- do - blood drip
	Membrane Diffusion	Clowes	200	3500	25	40-70	dr.blood-gas membrane	turb.flow, 100 mm.Hg req.
		Thomas	250	3000	0.5 x 20-30 = 10-2-/min.	30-80	used once	Turb., drip, steril. Film
	Gas Dispersion	Lillehei	200	650	?	40-100	low vol. capacity, interchange area, used once	turbulence, intense trauma
		Cooley-Eerland						

elastic tube on the output side of the pump during the intake phase of the pump, and a similar device occluding an elastic tube on the intake side of the pump during the output phase of the pump.

The constant-injection type of pump appears to be far more desirable. It consists of a helical tube made to rotate so as to make the upper end describe a circle. The direction of the circle described corresponds to the upward direction of the spiral, thus forcing the fluid up the tube by centrifugal force. It possesses one advantage over any other type of pumping device, i.e., it does not require either internal valves or external compression of an elastic tube in order to direct the flow of blood through it. There are certain obvious disadvantages, on the other hand, related to its mechanical construction and to the leading off of fluid from the upper end of the spiral tube.

The two common types of constant-flow pumps which have been employed in extracorporeal blood circuits are the roller type and the finger type. The finger-type pump utilizes the principle of series compression of a rubber or other elastic tube. A series of parallel metal arms, one after another, compresses a length of tubing. Any number of these arms may be used. When the last one in a row has compressed the tubing, the action proceeds again with the first arm. This type of pump is commercially available and has been used for the intravenous injection of fluids at constant, small flow rates, as well as in extracorporeal circuits. The mechanical construction of these finger-type pumps is such that they are not as suitable as the roller-type pumps for the production of rapid linear velocity of fluid in a tube.

In the roller-type pump, a cylinder is rolled over a rubber tube, compressing it and thus propelling the contained blood forward. Re-expansion of the elastic tube which follows the release of compression by the roller provides the sucking action of the pump. A drawback of the roller-type pump has been creeping of the rubber tube in the direction of the passage of the roller. This disadvantage was obviated by DeBakey by the attachment along one side of the tube of a rubber flange which is tightly clamped between semicircular metal bars. Two rollers mounted at the ends of a horizontally revolving bar successively compress the flanged tubing. As one roller leaves the rubber tubes, the second roller begins to compress them. Gibbon adapted this pump to the extracorporeal circuit using one to three tubes mounted one above another in each pump and driving the pump by a variable-speed electric motor.

2. Basic Aspects--Principles and Prototypes

One pump classification is based upon positive as opposed to non-positive displacement. Non-positive displacement or kinetic pumps move fluid in a continuous flow, but do not provide a positive internal seal against leakage. Therefore, delivery varies with back pressure or resistance. Positive displacement pumps have definite internal seals against slippage; since their output is relatively unaffected by variations in system pressure, they are more desirable where precise control of the amount of fluid movement is an inherent requirement.

Another classification of pumps separates those with fixed or variable displacements. In fixed displacement pumps, output may be changed only by changing pump speed. In variable displacement pumps, the geometry of the pump itself may be changed, so that output may be varied either by changes in stroke length or in pump speed. An additional division distinguishes between rotary (including the gear, vane, and piston types) and reciprocating varieties. The latter, in general, contain plungers which alternately trap and expel successive volumes of fluid.

a. Gear Pumps

Gear pumps are positive displacement pumps with few moving parts. They are simple and rugged. Fluid is carried in spaces between the gear teeth, and given direction by the meshing of teeth. Pumps of this general type are illustrated in Figure II-7 and include those with both external and internal gears, lobed elements, and screw types. In general, these have not been employed for extracorporeal circulation because of significant trauma to blood as well as pumping elements which are difficult to clean and are not disposable.

b. Piston Pumps

Piston pumps are capable of highest output pressures, and have a high efficiency, independent of back pressure. They may have fixed or variable displacements. Such pumps have been designed as reciprocating piston, rotary piston, and diaphragm compressor types (Fig. II-8). Of these, the diaphragm compressor, which is available in both fixed and rolling diaphragm versions, is the only one which has been employed in modern extracorporeal circuits.

c. Tubing Compression Pumps

Tubing compression pumps include most of the pumps currently used for extracorporeal blood propulsion. Among these are the finger or Sigmamotor type, the roller pump, and the pumps involving pneumatic, mechanical, or hydraulic compression of a tube (Fig. II-9). These are positive displacement pumps when they are occlusive. Their advantages lie in the easily replaceable and disposable pumping chamber (permitting the remainder of the pumping system to be unsterile) and in their low index of trauma to the blood.

d. Vane Pumps

Vane pumps consist of a rotor mounted in a housing with vanes fitted into slots in the rotor (Fig. II-10). The rotor revolves on a shaft which is mounted eccentrically to the housing. The vane tips slide in and out of the rotor to create closed rotating chambers. Both variable and fixed displacement models are available.

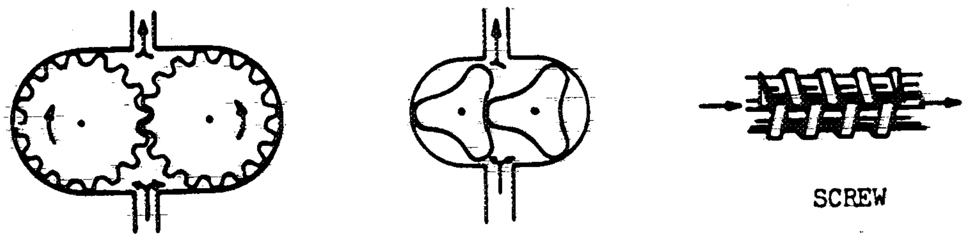


Fig. II-7 Gear Pump - Schematic Diagram Illustrating External Gear, Lobed-Element and Screen Pump Varieties

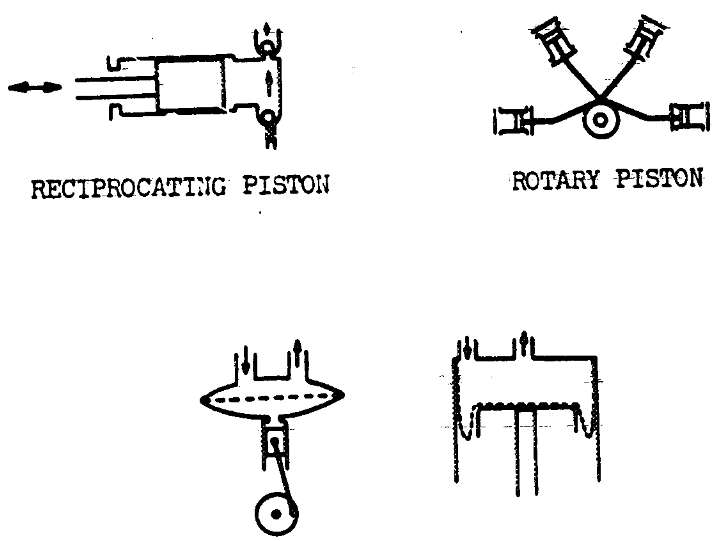


Fig. II-8 Piston Pump - Reciprocating, Rotary, and Diaphragm Types

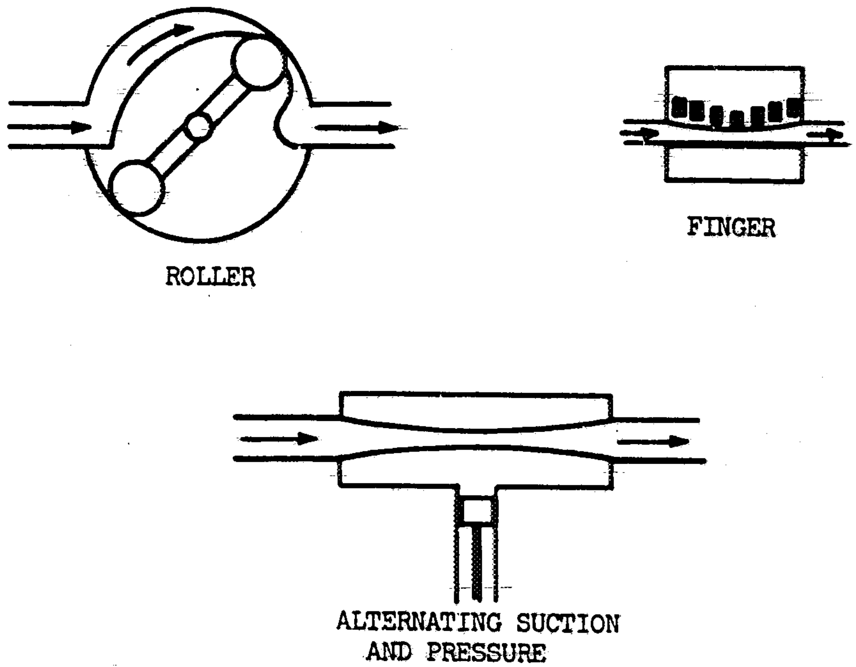


Fig. II-9 Tubing Compression Pump

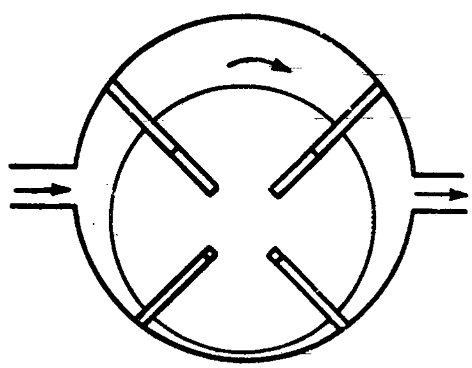


Fig. II-10 Vane Pump - with Fixed Positive Displacement

e. Non-positive Displacement or Kinetic Pumps

Non-positive displacement or kinetic pumps include propellers and other pumps of the centrifugal or axial flow type. In general, these operate at high velocities and have not been used for extracorporeal circulation because of the development of vortices, cavitation, and subsequent high rates of hemolysis.

3. Desirable Characteristics for Extracorporeal Circulation

Requirements which have been described for an ideal extracorporeal blood pump include:

1. Minimal trauma to blood. This implies a smooth, non-wettable inner surface without abrupt diameter changes, wide, short orifices and no turbulence.
2. Positive displacement, implying insensitivity to load or resistance.
3. Variable displacement and speed.
4. No internal valves.
5. Expendable pumping chamber, which can be heat sterilized.
6. Pulsatile, or intermittent, output.
7. Simple adjustments of both displacement and speed.
8. Continuous measurement of output. This is automatically fulfilled by positive displacement pumps where the pumping rate is known.
9. Some form of manual operation, in the event of power failure.
10. Minimal priming volume.
11. Reasonable cost.
12. Simple maintenance.
13. Quiet operation.
14. Explosion-proof motor.

There is still a wide divergence of opinion as to the relative merits (for clinical work) of the roller, finger, diaphragm, and external pneumatic, hydraulic or mechanical compression pumps. All have been utilized in large clinical series, including prolonged perfusions, with essentially equivalent success. Certainly, the relative advantages and disadvantages of each do not appear to argue convincingly in favor of a pump type at this time.

One important consideration may be studied in Table II-2. This compares data (obtained from the literature) as to the rate of hemolysis while pumping in vitro systems. Roller pumps appear less traumatic than finger or diaphragm pumps, in general. Based on these data, the least traumatic of the currently available pumps are the new springloaded rollers, and the Bellofram, or rolling diaphragm type. Some other pertinent characteristics of these pumps are compared in Table II-3, which emphasizes their inability to meet some of the criteria which have been listed. See Table II-4 for statistics on complete heart-lung systems.

TABLE II-2

COMPARISON OF IN VITRO HEMOLYSIS FROM THE LITERATURE

Author	Year	Plasma Hb. (Method of reporting)	Flow Rate (L/M)	Finger Model	Plasma Hb.	Roller Model	Plasma Hb.	Dia-phragm	Plasma Hb.
McCaughn	1957	Mgm. free Hb/hr.	1.75	T-6S	1500	Mark-occl.	400		
Hodges	1958	Mgm. %-after 2 hrs.	1.5	TM-2 Occl.	99	Mark II			
						Occl.	84		
				Non-occl.	76	Non-occl.	96		
Cahill	1959	Mgm. free Hb/100 ml/hr.	0.2	?	20	Leonards-(occl)	2.7	Dale-Schuster	3.5
						Herrik (non-occl.)	2.8	Sindelar	1.4
								MacNeil	15.17
Breckler	1959	Index of Hemolysis	3.0	?	1.334	DeBakey	0.173		
						UPI	0.043		
Cappelletti	1961	Index of Hemolysis	0.9	TM-2	2.00	Mark	0.55	Dale-Schuster	1.14
			2.0		1.02	DeBakey	.37		
								Dennis	0.93
Brown	1961	Index of Hemolysis	2.0	T6S	0.033	Herrik	0.004	Bellofram	0.008
Esmond	1961	Index of Hemolysis	4.0			Esmond	0.12		

Index of Hemolysis = added gm. of free Hgb./100 l. pumped, or added mgm. Hgb./100 ml. pumped.

COMPARATIVE ABILITY OF CURRENT PUMPS TO FULFILL SOME "DESIRABLE CHARACTERISTICS"

PROPERTY	PUMP TYPE			
	Finger	Roller	Diaphragm	Ext. Tube Compression
1. Minimal Trauma	See Table II-1			
2. Positive Displacement	If occl.	If occl.	Yes	Yes
3. Variable Displacement	No	No	Some models	Yes
4. No Internal Valves	Yes	Yes	No	Yes
5. Expendable Pumping Chamber	Yes	Yes	No	Yes
6. Pulsatile Output	No	Yes	Yes	Yes

TABLE II-4

PARTICULARS OF VARIOUS HEART-LUNG APPARATUSES

COMPLETE SYSTEMS

Type	Perfusion Volume, 1/min.	Volume Capacity ml.	Number of Parts	Hours to Clean	Hours to Assemble	Steril-izing	Instrumen-tation
Natural human	30	1000	--	--	--	--	--
Ideal	8-10	1500	min.	dispos-able	quick, simple	auto-clave	none or foolproof
Gibbon-Mayo	6	4000	200	3-4	3	formalin 12 hours	vol. control
Mark	4-5	4500	150	2-3	3	autoclave	--
Crafoord-S.	5	3000	70	1	1	ethylene oxide	vol.control, flowmeter
Kay-Gross	6	3000	230-250	2	2	autoclave	O_2 pressure
Dennis	3	1500	60	1	1/2	autoclave	vol.control
Clowes	6	4500	150-200	3-4	3-4	Warexin 2 hours	--
Thomas	6	4000	--	1	2-3	ethylene oxide	--
Lillehei	5	1000	50	1/4	1	autoclave	--

D. Intracorporeal Pumps--The Artificial Heart

Recently, investigators have also concerned themselves with the problem of the heart beyond repair. Such organs will require long-term "paracroporeal" support or total replacement. This need could be met either by transplantation of another biologic heart, or by a mechanical substitute. A mechanical implant appears to have these theoretical advantages over biologic transplants: no immune rejection mechanisms, minimal problems of supply, sterilization and storage. However, presently available pump designs do not yet adequately meet all of the requirements for chronic implantation.

Early work in this field was performed in the 1930's by Gibbon and by Barcroft who used external hydraulic compression and rotary pump systems. Most recently, Salisbury, Kirby, Kusserow, Saxton, Kolff, Hastings, McCabe, Liotta, and Seidel have experimented extensively with long-term reliance on pumps basically similar to those used for temporary extracorporeal support. In addition, newer designs tested include the rolling diaphragm, pendulum, and centrifugal pumps. In these studies, several animals have survived for many hours following removal of the heart and substitution of a mechanical pump.

Certainly the problems in this sphere do not appear insoluble. However, the direct substitution or intermittent use of these devices as circulatory augmenting units for prolonged space flights, other than their use under emergency conditions, does not appear to be consistent with practical life support systems design.

E. The Artificial Kidney

The more advanced extracorporeal artificial organ which is in actual clinical experimental use today is the artificial kidney. Patients with chronic uremia and up to about 85 percent renal failure are actively being treated at the artificial kidney clinic at the University of Washington in Seattle. Without this treatment, the life expectancy of these patients can be defined almost in terms of weeks. This work then represents a significant advance in the state of the art of artificial organs and artificial organ systems.

The artificial kidney, or hemodialyzer, makes possible the purification of blood by the removal of waste materials and introduction of substances to restore electrolyte balance and nutrition. It is, therefore, a two-way process in which materials are both removed and introduced into the circulation. It can be used to rid the body of toxic materials and also to introduce nutritive chemicals or drugs into the body. The artificial kidneys in use are reliable, tested instruments which have evolved after much clinical use.

1. The Development of Hemodialysis

Of all the instruments used to artificially supplement the physiological and biochemical processes of the body the artificial kidney has behind it the most years of development and testing. The principle of the artificial kidney was conceived in 1914 but it was only in the past 15 years that Kolff, Alwall, Skeggs and Leonards and others proposed various instruments applicable to humans.

2. The Process of Hemodialysis

Most of the artificial kidneys now in use routinely utilize the principle of dialysis. This process consists of the passage or diffusion of low molecular weight substances through a semipermeable membrane. Usually the membrane which is used is specially prepared cellophane. This operation is illustrated in the presentation of the various types of artificial kidneys later in this section.

3. Technique of Hemodialysis

No specialized facilities are required for accomplishing hemodialysis. However, specially trained personnel are needed to perform it.

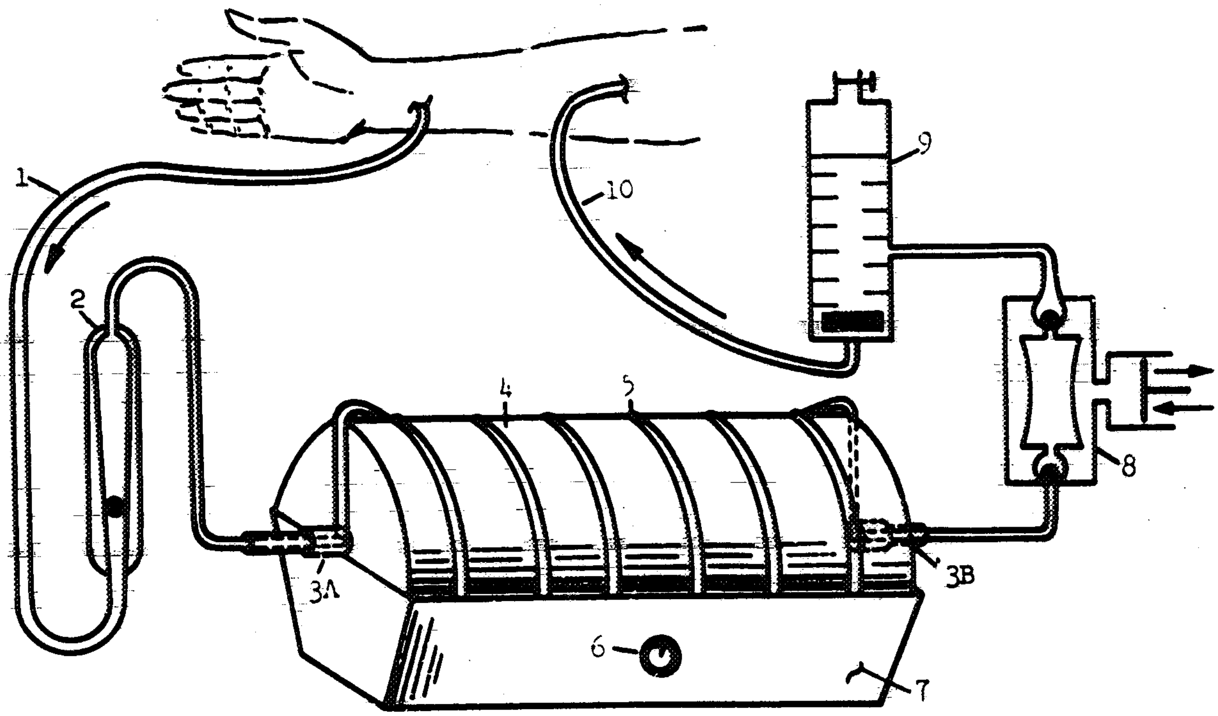
Careful clinical and laboratory examinations are given to detect renal, hepatic, cardiovascular and other defects. Hypoproteinemia and edema should be eliminated before artificial kidney treatment. The urea and non-protein nitrogen levels of the blood and other results of biochemical blood tests must be known. The coagulation time, bleeding time, and the prothrombin index are particularly important. A careful examination of the cardiovascular system and of the functional state of the liver will assure the favorable outcome of hemodialysis.

Hemodialysis must be conducted under strict observation of the patient's condition. The skin color, rate and character of respiration, pulse, arterial pressure and temperature are noted every 15 minutes. The urea level of the blood, the coagulability of the blood, the hematocrit reading and the CO_2 binding power are determined every 30 minutes. The saline solution is simultaneously analyzed for the levels of the electrolytes, urea and creatinine.

The average time of hemodialysis is 5-6 hours.

4. Kolff Artificial Kidney (Fig. II-11)

The Kolff artificial kidney consists of a cylinder of metal mesh. Cellophane tubing one inch in diameter, with a total length of one hundred feet, is wound on the cylinder, which is 110 cm high and 60 cm in diameter, and is submerged in horizontal position in a tank containing one hundred liters of saline solution. This solution bathes the lower half of the cylinder which makes one rotation about its axis every 2 seconds. Under the influence of the rotary motion the blood inside the cellophane tube passes in the form of a thin layer between two semipermeable walls. When the cylinder makes a complete revolution, the semipermeable membrane is completely bathed by the dialyzing solution.



1. POLYVINYL TUBE TO RADIAL ARTERY;
2. FLOWMETER;
3. ROTORS EFFECTING CONNECTION BETWEEN
   (A) INFLOWING AND
   (B) OUTFLOWING STREAMS
4. CYLINDER OF METAL MESH;
5. CELLOPHANE TUBE THROUGH WHICH BLOOD CIRCULATES:
6. THERMOMETER AND THERMOSTAT TO HOLD THE TEMPERATURE AT 37° C.;
7. DIALYZER TANK;
8. PUMP;
9. AIR AND CLOT TRAP;
10. EMERGENCE OF BLOOD.

Fig. II-11 Kolff Artificial Kidney

After the apparatus has been prepared for use, a polyvinyl chloride tube with its end connected to a flow meter is inserted in patient's radial artery. The flowmeter is connected with the cellophane tube wound spirally around the cylinder. Contact between the rotating cylinder and the fixed parts of the flowmeter is provided by a pair of plastic rotors. There is a similar device at the other end of the apparatus permitting the use of a pump to return the blood after dialysis to the patient's venous system. The pump is connected to a receiver containing a filter to trap blood clots and air bubbles. The blood is returned by a polyvinyl chloride tube to the patient's basilic vein.

The cellophane tubes used in the Kolff apparatus are sterilized by boiling twice for three hours each, changing the water once. The polyvinyl tubing, the pump, and the two rotors, are boiled for an hour in an autoclave at 120° C. and then thoroughly dried. All the tubes are used only once to avoid the danger of so-called pyrogenic shock.

A systemic study was made of the disposable Kolff coil kidney by Whittembury, et al. Dialysance and ultrafiltration were studied with varying temperatures, rate of flow of rinsing fluid, rate of flow of blood passing through the kidney and outlet pressure of the artificial kidney (venous pressure).

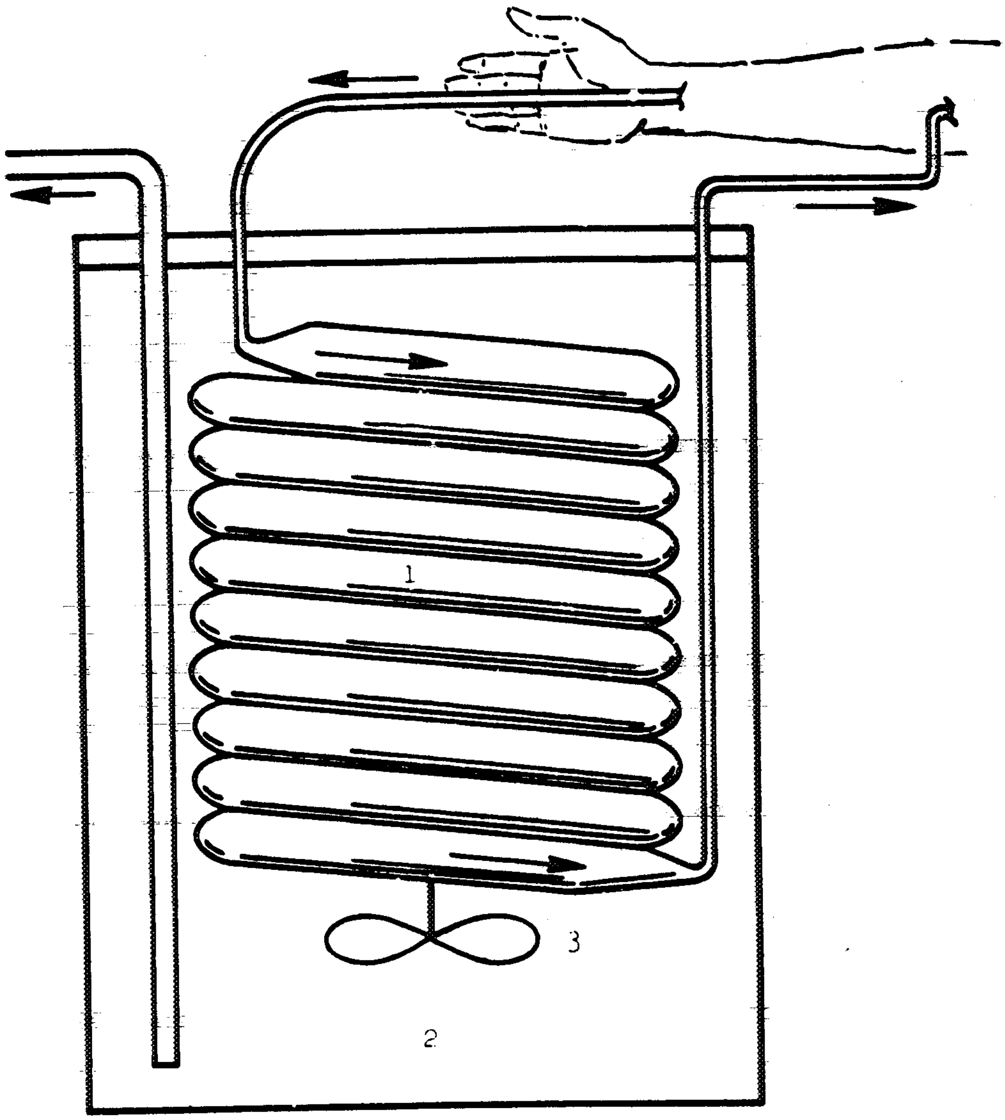
It was found that temperature of the rinsing fluid had no important effect upon dialysance. The optimal rate of flow rinsing fluid was approximately 8 liters per minute and the optimal rate of blood flow was about 0.2 liters per minute. Increasing venous pressure raised the ultrafiltration rate without significantly increasing dialysance. It was concluded by the authors that the Kolff kidney is an efficient instrument for dialysis and ultrafiltration.

5. Alwall Artificial Kidney (Fig. II-12)

The Alwall artificial kidney consists of a cylinder with cellophane tubes wound around it. This cylinder, in the vertical position, is completely surrounded by an outer cylinder containing a solution of electrolytes. A special impeller in the lower part of the apparatus keeps the solution in constant motion to maintain the proper rate of dialysis. The narrowness of the tubes and other improvements eliminate the need for a pump. The blood enters the artificial kidney from the radial artery and is returned to the patient's basilic vein. The tubes have a very large dialyzing surface area (16,000 cm^2) almost as great as the total surface area of the capillaries in the glomeruli of the human kidney (15,000 - 20,000 cm^2).

6. Lowsley and Kirwin Artificial Kidney

Two new types of artificial kidneys were proposed by Lowsley and Kirwin in 1950. The first type was based on the parallel flow of the blood and the electrolyte solution, the second on their counter-current flow. The Lowsley-Kirwin apparatus was the first to use cellophane sheets in strip form instead of cellophane tubing, thus making maximum use of their dialyzing surface. In the model with parallel current flow of blood and solution, the dialyzing



1. Cellophane tube with blood
2. Electrolyte solution
3. Impeller

Fig. II-12 Alwall Artificial Kidney

surface of the cellophane strips was 462 inches^2, while in the countercurrent model it was 720 inches^2. Lowsley and Kirwin showed that the rate of urea removal from the blood by dialysis was a maximum if the thickness of the membrane did not exceed 0.001 inch and that the higher the urea blood level, the larger the amount that could be removed by dialysis.

7. Skeggs - Leonards Artificial Kidney (Fig. II-13)

The Skeggs-Leonards "sandwich kidney" consists of plastic plates ground on both sides, of variable X number, between which two sheets of cellophane are spread out, creating a capillary blood film, while the dialyzing fluid is passed in countercurrent flow through the grooves along the membranes. Both flows are maintained by pump action.

8. Müller Artificial Kidney

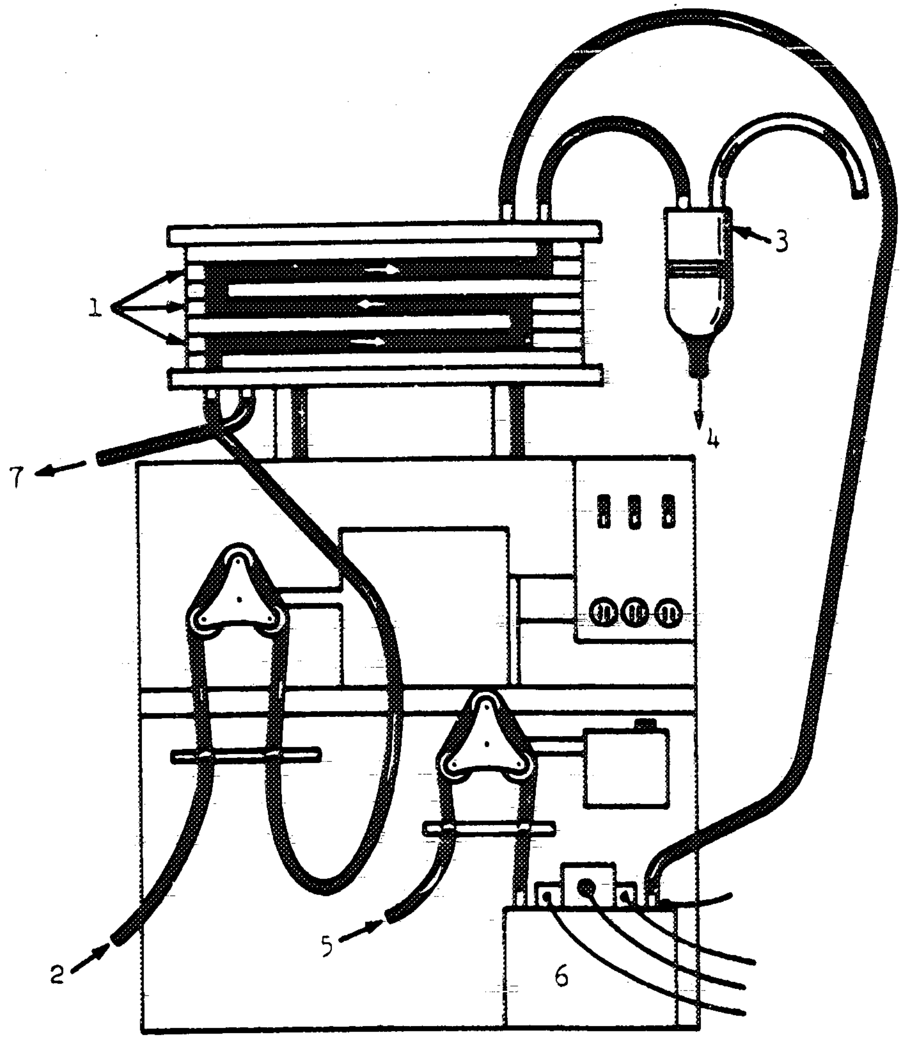
This design uses a hose, thus preventing stasis in the blood circulating through the apparatus. The blood in the tubes is washed by the countercurrent dialyzing liquid. The apparatus consists of the dialyzer itself and a thermostat which holds the saline solution, keeps it in circulation, and maintains it at constant temperature. The rate of circulation and the temperature may be set as desired. The dialyzing surface area is 0.9 m^2. There is a lavage channel 11.5 m long between the inner cylinder and the outer cylinder covering it. In this channel is the dialyzing tube, made of very thin-walled cellophane. The lavage channel is so designed that the lumen between its wall and the dialyzing tube shall not exceed 300 m in radius and only a very thin film of blood is treated. The smallness of the lumen means that only a small amount of blood is required to fill the system. Usually 500 ml of blood is enough for the entire blood circulating system. See Figure II-14.

9. Improvement in Kidney Design

Attempts have been made to design an artificial kidney which is automatically monitored. The preliminary report on "EMACK" (electronic apparatus for coil kidney) by Brennand,and "A Portable Artificial Kidney" (1960) can be cited in this regard. This trend is anticipated to continue with a fully automatic and more compact unit ultimately being evolved. The outlook for automation of the artificial kidney is favorable but whether the renal module could be packaged in a size, shape and arrangement to lend itself for use in space requires further investigation.

The engineering problem of designing an efficacious blood dialyzer is defined by the following requirements:

1. Large effective surface, i.e., large exchange area between blood and dialyzing fluid.
2. Development of a hemostatic head in a thin film.



1. HEMODIALYZER WITH CONSTANTLY CIRCULATING SALINE SOLUTION AND BLOOD IN CELLOPHANE SHEETS.
2. ADMISSION OF VENOUS BLOOD
3. BUBBLE AND CLOT TRAP
4. EMERGENCE OF BLOOD
5. ADMISSION OF DIALYZING LIQUID
6. HEATER
7. OUTLET OF USED DIALYZING LIQUID.

Fig. II-13 Skeggs-Leonards Artificial Kidney

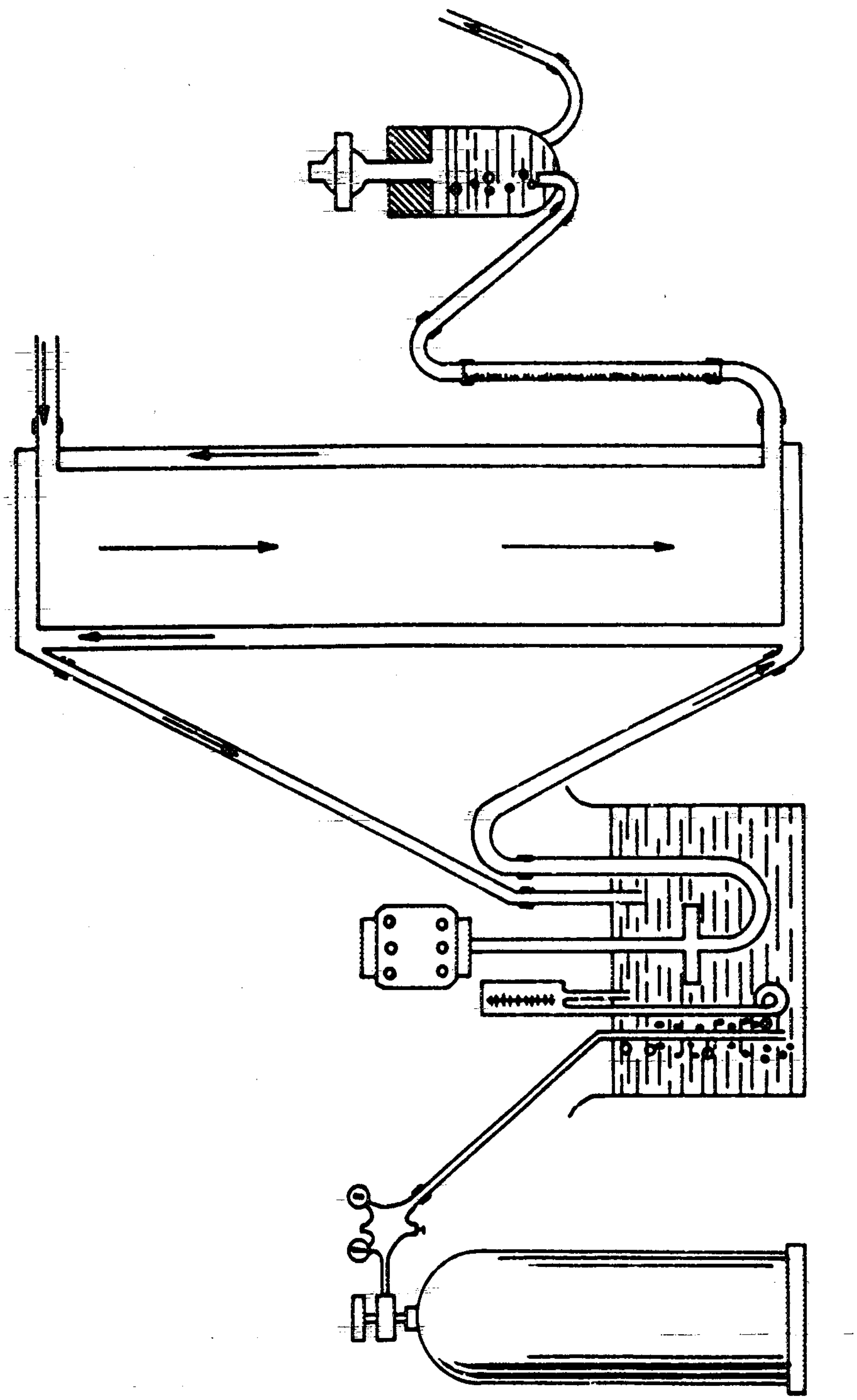


Fig. II-14 Müller Artificial Kidney

3. Uniformly high concentration differential between blood and dialyzing fluid (large volume of blood circulation with frequent renewal of solution).
4. Small priming blood volume.
5. Low internal resistance.
6. Laminar blood flow without formation of pools, to prevent coagulation in the apparatus and/or excessive heparin consumption.
7. Avoidance of wall rugosities to preserve cellular blood constituents; polyethylene and polyvinyl chloride as material for connecting tubes and fittings.
8. Variable pressure differential between blood and dialyzing fluid, i.e., ultrafiltrations effect variable as required (limited expansibility of blood tubing.)

There are definite areas where improvements will be and need to be made the future. These are:

1. Cannula kidney coupling
2. Optimizing hemodializer design
3. Pre-packaged blood tubing and cellophane envelope
4. A patient monitoring system
5. A new hemodialyzer membrane
6. Methods of supplying hemodialysis fluid

F. Conclusions

The artificial organs which have been discussed are the heart, lung and kidney. It is more likely that the heart-lung machine will evolve into a more refined form with continued research and development into a reliably functioning instrument for use on prolonged space flights or extraterrestrial space probes. The artificial kidney can be engineered to a more compact and portable form than now exists. However, because of the nature of the artificial kidney, this device, which by design must use large volumes of dialyzing fluid, would most likely not be necessary or capable of utilization in space flights to augment the physiology of man. Most likely the artificial kidney would attain its best utilization in an orbiting space station.

The use of these instruments, however, depends upon the couple between the instrument and man. This problem, although currently adequately solved by the use of indwelling synthetic catheters, still presents a major problem for man-machine integration in an extraterrestrial milieu.

It appears that, for the present, the most promising use of artificial organs is in their use as research tools in providing a better understanding of the basic physiology of man and how this will be affected when subjected to the changing environmental conditions in space research. The real significance of research into artificial organs lies in their use as experimental analogs for substitution into test conditions for evaluation without risking human life. Research into mathematical models of human system (see Section VI) which can be verified by animal experiments will lead to the development of such a physical analog-artificial organ.

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III. HYPOTHERMIA

A. Introduction

The purpose of this report is to evaluate potential future applications, to the space effort, of hypothermia, related physiologic changes and associated techniques. This has been done with particular emphasis upon potential roles of hypothermia as applied to:

a. Reduction of life support requirements for humans during extended periods of inactivity, in flight or on planet surfaces.

b. Added protection for these personnel in the extraterrestrial environment.

c. The same functions, but as an emergency back-up in event of failure of the primary life support system.

d. Inclusion in the medical-surgical modules of space travel and extra-terrestrial habitation.

As a part of the complete evaluation, definite consideration is given to terrestrial fall-out from continued research in space-oriented programs.

This report has been prepared from an extensive search of the literature, both domestic and foreign; examination and evaluation of current techniques, materials, and equipment; and direct communication with leading clinicians and researchers in the field.

In order to present a proper perspective of this topic, in the first portion of this report we will define terminology, review the history and physiologic effects of hypothermia, and discuss present techniques and applications. In the latter portion, we will analyze the feasibility of utilizing known and expected techniques of hypothermia and other methods of producing hypometabolism for various applications in the space effort. Conclusions derived from the study complete this section.

B. Definitions

As is usually the case when innumerable people of multiple nationalities and varied training are involved in a common field, the terminology used is often confused and misleading. For purposes of consistency, we have adopted the following definitions:

Hypothermia: Reduced body temperature, in toto or in part, in non-hibernating homeothermic species, induced by any method.

Total Body Hypothermia: Total body reduction of temperature.

Local Hypothermia: Reduced temperature of portions only of the body-areas or organs.

Degrees of Hypothermia:
1. Light: 37° - 32° C.
2. Moderate: 32° - 26° C
3. Deep: 26° - 20° C.
4. Profound: Under 20° C. (Little, 1959)

Artificial Hibernation: Hibernation induced in a normally hibernating species at a time when that species would not normally go into that state.

Natural Hibernation: Naturally occurring hibernation in a normally hibernating species (Juvenelle, 1954).

Throughout this section, the centigrade system will be used for temperature measurements. Recognizing that there is no single core temperature, esophageal temperatures at heart level will be utilized wherever possible for reasons given below.

C. History

The use of hypothermia in medicine dates back to Hippocrates, who advised application of cold as an analgesic and to check hemorrhage (Armstrong-Davison, 1959). Avicenna listed cold as one of the lesser stupefacients (Gruner, 1930). Refrigeration analgesia was advocated during the Renaissance and later by Baron Larray, Napoleon's Surgeon General (Little, 1959). In 1800, James Currie used cold water immersion and application in the treatment of "Fever and other Disease" (Curie, 1805). In 1866, ether spray was introduced for surface analgesia and, later, ethyl chloride also for the same purpose (Little, 1959). In 1872, MacKenzie was using cold for local anesthesia during laryngoscopic examinations (MacKenzie, 1872). Many more similar applications are extensively recorded. Experimental total body hypothermia was studied by John Hunter (Armstrong-Davison, 1959), Simpson & Herring (1905), Tuffier (1920), Crafoord (1935), and others. We note that Haymens did the first work with the extracorporeal pump-oxygenator in 1921 (Trede, Chir et al, 1961).

The first modern application of hypothermia to clinical pathology was performed by Temple Fay in 1940 in the treatment of malignant disease, with some regression but no reversal of the growths (Fay, 1959). Talbott in 1941 utilized this also in the treatment of psychotic patients (Talbott, 1941). McQuistan introduced the technique in the treatment of cyanotic heart disease in 1949 (McQuistan, 1949) and in 1950, Bigelow and co-workers suggested using total body hypothermia to achieve complete circulatory occlusion of the heart for intra-cardiac surgery (Bigelow, Callaghan & Hopps, 1950). A key break-through in regard to modern cardiac surgery was accomplished by Gollan in 1952, who coupled the use of the extra-corporeal pump-oxygenator with hypothermia (Gollan, Blos & Schuman, 1952). Another approach to total body hypothermia, that of pharmaceutical hypothermia, was strongly advocated by Laborit and Huguenard in 1951 (Laborit, 1951) and has been vigorously pursued since in Europe, principally in France. It is apparent, then, that hypothermia per se is not a new technique. However, intensive clinical application of this technique, particularly in surgery, has been accomplished only within the past two decades.

D. Physiologic Effects

Before reviewing the physiologic effects of hypothermia, it is necessary to point out the temperature differentials that occur within the body in this state. As expected, with externally cooled subjects, there is a marked temperature gradient between superficial and deep structures (Hegnauer & Penrod, 1949). When direct blood stream cooling is used, temperature differentials are less, but still significant (Ruhe & Horne, 1955). In the latter instance, the individual organ temperature is a function of its active blood supply and metabolic rate. Ellison (1961) reports an increasing temperature level from esophagus to brain to muscle. Brain temperature may be 6° to 8° C. higher, and skeletal muscle temperatures higher still (Zinng & Kantor, 1960; Civalero, Moreno et al, 1962). Rectal temperature is very inaccurate. Esophageal temperature, reflecting the temperature of cardiac blood and being one of the most accurate accessible sources of core temperature, is accepted as the best indicator (Cooper, 1959; Severinghaus, 1959).

1. General Metabolism

Metabolic rate as measured by oxygen consumption is markedly decreased under hypothermia (Pratt & Collins, 1956; Reemsta, Martin et al, 1958) once the initial stress response is passed or this response avoided by use of drugs and rapid blood stream cooling. The fall is reported as both linear (Bigelow, Mustard et al, 1954) or exponential (Fairley, 1961) in regard to temperature fall. For practical purposes, however, general metabolism is decreased by 6 to 7% /°C. drop in temperature (Marcy, 1961; Rosomoff, 1956). Representative percentages of normal rates are:

50% at 30° C. (Stephan & Dent, 1962; Young, Sealy et al, 1959)

30% at 25° C. (Loughead, 1961; Botterell, Lougheed et al, 1955)

15% at 20° C. (McClelland, 1956)

6% at 10° C. (Padhi, Rainbow et al, 1961)

3% at 4° C. (Cockett & Beehler, 1962)

Two major points are to be stressed. First, the most useful physiologic result of hypothermia is a state of <u>hypometabolism</u>. This is the basis for the majority of its current medical-surgical applications, and also the reason for its consideration in space personnel logistic and protection problems. Second, metabolism is not completely eliminated in the low levels of profound hypothermia. Adequate perfusion is necessary even at these low levels (Gollan, Blos & Schuman, 1952: Yeh, Ellison et al, 1961).

2. Cardiovascular

Cardiac rate decreases as temperature falls, with cessation of cardiac activity near 15° C. (Fay, 1959; Stephan & Dent, 1962) in man. This bradycardia appears to be a direct cold effect upon the sinus pacemaker, independent of vagal or atropine activity (Koons, 1957). Both systole and diastole are prolonged as a result, with particular effect upon the isometric relaxation phase (Koons, 1957). The physio-chemical processes during excitation in the sinus node and during myocardial repolarization, having a high temperature coefficient, are more severely impaired, whereas the excitation spread through the remainder of the conduction system, which has a low temperature coefficient, is less affected by cold (Blasius, Albers et al, 1961). Cardiac output falls (Dripps, 1955; Lucas, 1959), although the maximum stroke volume has been reported to remain constant in the dog over a wide temperature range (Reissman & Van Citters, 1956). Myocardial contractility, however, is not impaired, as indicated by an increase in ventricular contractile force (VCF) which is recorded as reaching a peak of 185% of normal at 21° C. (Trede, Chir et al, 1961), and higher (Covino, 1958). Although the work capacity of the heart is decreased, it still exceeds the requirements of the body (Reissman & Van Citters, 1956). The EKG changes have been extensively recorded. The P wave, PR, QRS complex and QT durations are prolonged, reflecting the slowed conduction rate (K'o-Ch'in et al, 1958; Lange, Weiner et al, 1949; Callaghan & McQueen, 1954). The ST segment may be elevated or depressed (McClelland, 1956; Boere, 1956; Boere & Derlagen, 1957).

Auricular fibrillation has been one of the major problems in hypothermia, frequently occurring in man below 26° to 28° C. (Gray, 1958; Veghlyi, 1962; Keele, 1957). Multiple causes of the ventricular fibrillation have been cited - acidosis, sudden elevation of pH from abnormally low levels, anesthetic agents, poor coronary flow, etc. (Kaplan & Fisher, 1958; Swan, Virtue et al, 1955; Lucas, 1959). Clearly, however, myocardial irritability increases. Covino & D'Amato (1962) identify the circus movement as the mechanism of the fibrillation, in which the refractory period is prolonged proportionately longer than the conduction velocity. Electrical defibrillation is the common method of reverting the heart to normal sinus rhythm (Brock & Ross, 1955). Maintenance of a constant pH, use of quinidine, potassium and Wyamine are also recommended for prevention and/or treatment of the ventricular fibrillation (Swan, Virtue et al, 1955; E. Carney, Ross et al, 1960; Covino, 1958).

Blood pressure usually rises in light and moderate hypothermia, but definite hypotension occurs below 26° C. (Juvenelle, 1954; Rosomoff, 1956; Koons, 1957; Ankeney, Viles et al, 1958). Peripheral resistance itself increases as the result of vasoconstriction in response to cold blood (Pratt, Wolff et al, 1961; Lucas, 1959). With this vasoconstriction, physiological A-V shunts are created as a major portion of the circulating blood by-passes the capillary beds (Koons, 1957).

3. Blood

The most striking and significant effect of hypothermia on blood is the marked increase in viscosity (Overbeck, 1961). This has proven to be one of the major obstacles in maintaining adequate perfusion at profound hypothermic levels (Neville, Kameya et al, 1961; Marion, Gounot et al, 1960; Brown & Smith, 1963). Andjus (1955) and Smith (1955) have demonstrated that levels near 0° C. are compatible with survival of non-hibernating animals, if adequate perfusion is maintained. As will be noted later, oxygen dissolved in plasma at these low temperatures and/or under hyperbaric conditions is adequate to meet the metabolic needs. Low molecular weight dextran has been used successfully in animals as a blood replacement to alleviate the viscosity problem (Overbeck, 1961). Brown and Smith (1963) have similarly used normal saline solution with success. However, successful clinical replacement will require a solution with the required specific osmolarity characteristics.

Impairment of the clotting mechanism occurs at deep and profound hypothermic levels, as exhibited by prolonged bleeding and clotting times (Brown, 1956; Koons, 1957). The platelets drop to very low levels, 50% or below at 16° C. (Simonovic, Adamec et al, 1960; Andersen, 1961). Red blood cell concentration, hemoglobin concentration, and hematocrit increase, the result of inter-compartmental fluid shifts, or of retained plasma in the peripheral vasculature being removed from active circulation (Munday, Blane, et al, 1958; Dripps, 1955; Lofstrom, 1957). The leukocyte count falls (Marion, Gounot et al, 1960; Lofstrom, 1957), the result of sequestration in the liver, spleen and possibly bone marrow, or from layering of these cells along the vascular walls (Dogliotti, Ciocatto et al, 1961).

4. Pulmonary

Respiratory rate and depth are depressed with drop in temperature, although this fall is not linear (Lange, Weiner et al, 1948). Respiration ceases at 22° to 28° C., depending to a great extent upon the type of anesthesia used. (Osborn, 1953; Michel & Edmark, 1960; Gray, 1958). Cooper (1959) cites the fact that the respiratory center remains normally responsive to carbon dioxide even in the lower temperature ranges. Severinghaus, Stupfel et al (1957) report that the removal of carbon dioxide across the alveolar membrane is unhindered. Their work has also revealed that the anatomical and physiological dead space is increased, apparently from bronchodilatation.

5. Biochemical (Blood and Tissue)

The oxygen dissociation curve shifts to the left, with the oxygen bound more tightly to the hemoglobin (Juvenelle, 1954; Gray, 1958; Fairly, 1961). This shift, however, can be counteracted somewhat by increasing the carbon dioxide (Gray, 1958; Fairly, 1961). As the temperature falls, the amount of oxygen dissolved in the plasma increases to such a degree that in profound hypothermia, the dissolved O_2 alone is sufficient to supply the tissue requirements (Boerema, Meyne et al, 1960; Brown & Smith, 1963). Ebert, Greenfield et al (1962) report that at 12° C., all the oxygen utilized is obtained from solution. The amount of carbon dioxide in solution likewise increases with lowered temperatures (Boere & Derlagen, 1957; Fairley, 1961). It is important to stress again, however, that individual organ oxygen debt can and does occur if adequate perfusion is not maintained.

Many conflicting reports in regard to blood electrolyte changes are recorded, undoubtedly due, in many cases, to technique and species variations. However, fall in serum potassium usually occurs, with most observers attributint this to a shift from the extracellular compartments (Koons, 1955; Munday, Blane et al, 1958; Dogliotti, Ciocatto et al, 1961). No significant changes of serum sodium or chloride are noted (Swan, Zeavin et al, 1953; Segar, Riley et al, 1955). However, serum calcium does increase, producing an increase in the calcium/potassium ratio (McMillan, Case et al, 1957). This latter increase is felt to play a significant role in the greater myocardial sensitivity.

Without assisted respiration, a serious respiratory acidosis occurs (Osborn, 1953; Axelrod & Bass, 1955), which some feel contributes to the increase of ventricular fibrillation, as previously noted. This acidosis can be well controlled with completely controlled respiration by the anesthetist. However, as lower temperatures are reached, a metabolic acidosis is encountered which is partially reflected by an increase in blood lactic acid, unless adequate perfusion is maintained (Neville, Kameya et al, 1961; Trede, Chir et al, 1961, Bernhard, Carroll et al, 1961).

6. Neurological

Hypothermia produces two physical changes in regard to the brain which have been used clinically. Brain volume is reduced to the order of 4.1% at 25° C. (Marcy, 1961; Rosomoff, 1959). As a result, the unoccupied intracranial space is increased significantly, 31.7% at 25° C. as reported by Marcy (1961), allowing the neurosurgeon more working space. In addition, the brain tissue is firmer, which also facilitates neurosurgical procedures.

Temple Fay (1959) reports the following sequence of loss of neurological function in patients during hypothermia: dysarthria and mental dullness below 34° C.; loss of phonation below 27° C.; and loss of pupillary light reflex below 26° C. EEG activity ceases at 18° to 22° C. (Zingg & Kantor, 1960; Lougheed, 1961).

Cerebral blood flow is reduced (Rosomoff, 1956) and oxygen consumption falls, being 33 1/3% of normal at 25° C. Rosomoff (1959) places the rate of reduced cerebral oxygen consumption at 6.7% per 1° C. fall. As expected, with the suppressed metabolism, cerebral glucose utilization is less (Adams, Elliott et al, 1957). Anand, Malhotra et al (1958) report also that acetylcholine and gluthathione utilization is decreased in the hypothalamus and frontal lobes, but increased in the temporal lobes. As in the myocardium, there appears to be an intracellular shift of potassium, which may be bound to mitochondria (Schwarz-Tiene, 1958).

Of clinical significance is the fact that stimulus threshold is lowered and duration of responses is prolonged (Cohn & Rosomoff, 1957; Chardon & Bonnet, 1958). Ordinarily innocuous stimuli may evoke a severe response, a situation of concern when dealing with epileptic subjects. The analgesic effect upon peripheral sensory nerves is well known. Peripheral nerve transmission ceases entirely at 6° to 8° C. (Juvenelle, 1954). The autonomic nervous system is similarly depressed, the parasympathetic portion being more sensitive than the sympathetic portion. Both are inhibited below 28° C. Koons (1957) feels that vagal activity may be inhibited due to reduced carotid body responses from the fall in blood pressure in addition to direct cold effect.

The foregoing changes are impressive. However, there is ample evidence that profound hypothermia is tolerated by the neurological system without sequellae if the perfusion rate meets its reduced but still necessary needs.

7. Renal

Renal changes occur in two major areas. Glomerular filtration rate (GFR) is reduced as a result of reduced renal blood flow and mean arterial blood pressure (Kanter, 1959; Jontz, Bonous et al, 1960). A dissenting note is heard in regard to this, however, in that Reemstma, Martin et al (1958) state that the reduced GFR is not related to arterial blood pressure. Urine volume is not significantly changed in proportion to the GFR, however, in that distal tubular function is inhibited, apparently a direct effect of cold upon the transport mechanisms. The reabsorption of water, sodium, and glucose is inhibited, as is potassium excretion (Kanter, 1959; Segar, 1958). The kidneys' ability to produce ammonia and, conversely, to acidify urine also is severely impared (Segar, 1958). Segar defines the resultant urine product as a glomerular filtrate which has undergone isosmotic reabsorption, but is otherwise unaltered by further tubular activity.

8. Liver

Hepatic metabolism is likewise reduced (Fairley, 1961). Bile volume decreases but the cholic acid concentration is not reduced (Fisher, Fedor et al, 1956). Fisher found an increase in liver NPN, but a decrease in glucose. Under 30° C., the liver cannot utilize blood glucose. However, fructose can enter the hepatic cells, and there be converted to glucose (Cooper, 1959). Of considerable clinical importance is the suppression of the detoxification ability of the liver under hypothermia. The half-life of drugs is prolonged many fold at deep hypothermic levels (Rink, 1956). Upon rewarming, the undetoxified portion of drugs previously administered is still quite active and may produce a severe cumulative effect.

9. Endocrine

Following the initial stress reaction, if encountered, thyroid activity, pituitary function, and ADH production in the hypothalamus are all depressed.

Insulin activity and production are likewise decreased (Cooper, 1959). The major emphasis in the study of endocrine effects of hypothermia, however, has quite naturally been placed on the adrenal glands. In that the initial result of cold is a stress reaction, this is a moderate increase of adrenal cortical activity. Below the point of this reaction, adrenal cortical activity falls, 17-hydroxycorticoid production and conjugation are depressed. This depression is not affected by added ACTH or surgery, nor is it the result of lowered blood flow alone (Bernhard & McMurray, 1956). Ostashoov (1961) has studied the role of ascorbic acid upon the hypothermic adrenal. He has found that the amount of ascorbic acid in the adrenal at deep hypothermic levels increases considerably, with a concomitant decrease in circulating ascorbic acid. By saturating animals with ascorbic acid, he observed a lack of adrenal hypertrophy in response to cold and noted the animals became more resistant to cold.

With the acknowledged risk of sacrificing continuity and readability, a large variety of general and specific physiologic effects of hypothermia has been presented. One of the major reasons for doing so has been to emphasize that hypothermia does not produce a smooth, uncomplicated progression of reduced body functions. On the contrary, the rate and types of changes vary significantly between different organ systems. In addition, the method itself - cooling - produces major barriers to the utilization of lower levels of hypothermia, among which are marked increase in blood viscosity and inhibition of temperature sensitive physio-chemical mechanisms. The wide spread clinical use today of moderate, deep, and increasingly profound hypothermia has only been possible through the development and use of refined devices and techniques. Discussion of these is included in the following section.

E. Methods

1. External Cooling Devices

The various methods available to produce total or partial body hypothermia are presented on the following pages in tabular form, with respective advantages and disadvantages.

TABLE III - 1

SURFACE COOLING

a. Ice bags

b. Water immersion

c. Refrigerated blankets

d. Cooled air

Advantages	Disadvantages
Relatively simple	Bulk and weight
Readily available	Marked cold stress reaction
No surgery required at mild and moderate hypothermic levels	Poor control and marked temperature drift
	High surface - core temperature gradient
	Danger of tissue cold injury
	Slow
	No perfusion control
	Personnel required

TABLE III - 2

DIRECT BLOOD STREAM COOLING -
USING EXTRACORPOREAL PUMP AND COOLING

a. Using Oxygenator

Advantages	Disadvantages
Rapid	Weight, bulk, and complexity
Good perfusion control	Aseptic surgery required
Good temperature control	Blood trauma in extracorporeal system
Avoids majority of cold stress reactions	Blood-gas interface with disc or screen oxygenators
Smaller body temperature gradients	Perfusion rate lower than with autogenous lung
Tissue cold damage eliminated	Highly trained personnel required

b. Using Autogenous (subject's) Lungs

Advantages	Disadvantages
As in II-2a; also	As in II-2a, except that
No blood-gas interface	Blood-gas interface is eliminated
Pulmonary complications reduced	Also,
	Double cannulization required

TABLE III - 3

BODY CAVITY COOLING

a. Colon

b. Peritoneum

c. Pleural

d. Gastric

e. Bladder

Advantages	Disadvantages
Simple in regard to externally available cavities	Primarily usable for local cooling only
	Very slow for total body hypothermia, when possible
	Surface cold injury
	Very poor temperature control
	Surgery required in some instances

TABLE III - 4

INDIVIDUAL ORGAN COOLING

a. By local perfusion

b. By cooling organ surface

Advantages	Disadvantages
Allows selective cooling	Limited use only
	Surgery usually required
	Surface cold injury with b

TABLE III - 5

PHARMACEUTICAL

Advantages	Disadvantages
Potentially simple to institute	Mild hypothermic levels only possible with present drugs
Can be self-administered (No additional personnel for this purpose)	Poor control of depth and duration
Minimal weight and cube	
Non-mechanical	
No surgery required	
No blood trauma from an extracorporeal system	

2. Electrical Stimulation of Hypothalamus (Experimental Use Only)

Rather than present further details of extracorporeal pump and oxygenator construction here, reference is directed to the section on artificial organs (II) in this publication.

Of the methods tabulated in this section, Body Cavity Irrigation and Electrical Stimulation of the Hypothalamus are not applicable to our purposes. Local organ cooling, such as regional brain perfusion, can be considered as a limited type of perfusion hypothermia discussed below.

The problems and disadvantages of surface cooling are impressive. The lack of control, the high body temperature gradients, marked stress response during induction phase, and absence of perfusion control are significant deterrents to its use in deep or profound hypothermia. However, it has been feasible to produce prolonged mild hypothermia with this method and in such a role can be considered in space logistic problems.

Direct blood stream cooling with the extracorporeal pump is the method of choice for deep or profound hypothermia. Using the subject's lungs offers the additional advantages of less blood trauma and a higher allowable perfusion rate. Speed and controlability are the prime factors with this general method in regard to its surgical use.

Pharmaceutical methods to produce hypothermia have not gained wide use, primarily because of the relative ineffectiveness of this method to produce a significant degree of temperature drop.

F. Current Clinical Applications

1. General Medicine

One of the oldest applications of hypothermia has been to combat febrile conditions; it is still widely used for this purpose. Colonic irrigation, surface sponging and refrigerated blankets are utilized. Although its role in the treatment of extensive burns is still in contention, local hypothermia is recommended in the treatment of less extensive burns. Wangensteen et al (1962) cite the effectiveness of gastric mucosal cooling in the treatment of gastric hemorrhage and ulcers.

Additional suggested uses have been to aid in the treatment of neonatal asphyxia (Miller, 1958), carbon monoxide poisoning (Craig, Hunt & Atkinson, 1959), severe antigen-antibody reactions (Vukobratovic, 1961) and multiple sclerosis, although not all of the latter uses have been fully evaluated by extensive clinical test.

2. General Surgery

Hypothermia has not gained wide acceptance in the field of general surgery. Pre-operative cooling of patients, local organ cooling (Cockett, 1960), differential cooling during chemotherapeutic perfusion for malignancy and institution of hypothermia during tuberculosis lung surgery (Dechene, 1957) have been utilized on a restricted basis. Some have advocated the use of hypothermia in the treatment of hemorrhagic shock. However, there appears to be no rationale for such usage.

3. Neurosurgery and Neurology

Mild and moderate hypothermic levels have been used in neurosurgery for some time to gain the advantages of firmer brain tissue and increased operative space (Callaghan & McQueen, 1954; Botterell, Lougheed et al, 1955). Both total body and selective brain cooling have been used (Fay, 1959; McMurrey & Bernhard et al, 1956). However, a distinct advantage from such cooling is yet to be proven from the standpoint of reduced morbidity and mortality. Wide use of hypothermia, however, is made in the treatment of head injuries to reduce cerebral edema and traumatic hemorrhage. For the same purpose, it is also utilized to prevent post-operative cerebral edema.

4. Cardiovascular Surgery

By far, the most extensive use of total body hypothermia has been in this field of surgery. It has been this application which has spurred the modern advances in total body hypothermia techniques. Surface cooling is still widely used for the less complicated lesions and preferred by many surgeons. In dealing with the more complicated lesions where longer interruption of circulation is required, extracorporeal cooling and pump systems have come to the fore. The double cannulization technique introduced by Drew et al to allow utilization of the patient's lungs promises to decrease the blood requirements and pulmonary complications encountered with various artificial oxygenators.

G. Protective Effects of Hypothermia

The basis for most of the protective benefits of hypothermia is the state of hypometabolism that results. Tissue protection from interrupted or reduced blood supply, physical trauma, hyperthermia and carbon monoxide intoxication have been cited above. However, extensive work has been conducted investigating other hazards whose adverse effects are similarly reduced by the use of hypothermia.

Many studies have been performed to evaluate the results of X-irradiation under conditions of hypothermia. Bloom and Dawson (1961) subjected mice to whole body irradiation with normally lethal doses. No deaths resulted in those animals which were at a temperature of below 30° C. at the time of exposure. An earlier study by Szilagy, Benko & Csernyanszky (1958) with mice at 15° to 20° C. produced the same result. F. John Lewis (1960) obtained 83% survival with rats at 0° to 10° C. using doses exceeding LD100 as rated at normothermic levels. Kuskin, Wang et al (1959), Hornsey (1956) and others report comparable results. Similar protection is reported in reference to gamma and cosmic radiation (Cockett & Beehler, 1962).

Increased tolerance to high g-forces has been demonstrated in centrifuge tests exposing mice to 2300 g for periods up to 15 minutes. Studies by Malette have demonstrated an increased tolerance to dysbarism (Cockett & Buhler, 1962).

Marcy (1962) reviews the work done demonstrating an increased tolerance to bacterial and viral infections. It is felt that this result is due to both the reduced growth rate of the pathogens and to the reduced oxygen needs (metabolism) of the tissues involved.

Exploitation of the above benefits in a hostile space environment is worth serious consideration, in that conventional protective measures may be neither possible nor effective due to weight restrictions, or to a situation where the degree of the hazard exceeds predicted levels.

H. Prolonged Hypothermia

In view of the consideration of using hypothermia on prolonged space missions for reduction of logistical loads, a brief discussion on the present state of prolonged hypothermia is in order.

In discussing prolonged hypothermia, it is well to note that very little research or clinical experience has been gained in the use of hypothermia for periods exceeding one week. Fisher, Fedor et al (1958) report the results of their studies involving periods of twelve hours. Lewis (1961) reports his experimental work with dogs at deep hypothermic levels extending to twenty hours. In the latter study, respiration but not circulation was controlled. The high survival rate in two of the groups (100% survival of five dogs receiving Reserpine; 71% survival of seven dogs used as Reserpine controls) were attributed to improved anesthetic and respiratory techniques, with possibly some benefit being derived from the use of Reserpine.

Temple Fay and others have maintained patients at mild hypothermic levels for periods of two weeks or more. At the temperature levels involved, the major adverse effects of hypothermia were avoided.

It is reasonable to assume that in order to obtain the best logistical advantage from hypothermia, a period of over one week at moderate to deep hypothermic levels should be utilized to gain enough weight and bulk advantage to justify its use for this purpose. It is hoped that continuing research in long duration hypothermia will be pursued to further clarify its ultimate role in reducing space life support load requirements.

I. Other Hypometabolic States

Our attention and interest should not be restricted solely to hypothermia. Although it is true that the use of cold is the only effective method available today of inducing marked hypometabolism, other induced or naturally occurring states of hypometabolism are of importance.

Drug-induced mild hypothermia has been previously cited. The well known "Lytic Cocktail" consisting of chlorpromozine, meperidine, and promethazine, has been extensively used. The effective agent is chlorpromazine, whose hypothermic capability apparently is due to peripheral vasodilatation. Although the hypothermic reduction of metabolism is relatively small, extreme interest continues in this method, particularly in Europe. (Gray, 1958; Veghlyi, 1962; Chesnokova & Agayev, 1958; Laborit, 1956; Alluaume, 1952; Dechene, 1957; Dundee & Mesham, 1954)

The clinically accepted drug propylthiouracil may also be included. However, the slow rate of effectiveness, relatively poor control, and restriction of primary action to the thyroid gland make it poorly adaptable to anticipated space needs.

Of great basic interest is the process of hibernation, which has been the subject of study for a great many people over a long period of time. The basic research in this area is of particular significance in attempting to identify, and perhaps isolate, the specific enzyme and other primary physiological differences which exist between hibernating and non-hibernating animals.

Many of the subtle differences have been identified. Some of the characteristics of hibernation are: the animals must be ready to hibernate; metabolism drops sharply before hypothermia develops; the temperature drops in steps; blood pressure stays up despite fall in pulse; cardiac, respiratory, nerve, and other vital functions continue to perform even at low temperatures

(1° to 5° C. in some species); and metabolism increases if body temperature falls below 0° C. (Lyman, 1961).

It is clear that hypothermia is the result, not a cause, of natural hibernation (Lyman, 1961; Popovic, 1956). When hibernating species are exposed to induced hypothermia, the physiologic responses at the various core temperature levels differ entirely from those occurring during natural hibernation.

Bigelow in Toronto has been particularly active in attempting to isolate the "hibernating hormone" of the ground hog. He feels such a substance is present in glandular tissue, which histologically resembles adrenal tissue, located in the axillae and mediastinum of the animal.

Of similar note is the process of estivation by which animals physiologically adapt to the environment of prolonged extreme heat and dryness of the desert. Swan (1963) is currently very interested in pursuing investigation of the antimetabolic agent which he believes exists in a concentrated form in such an estivating reptile in Africa.

It is reasonable to expect that basic research of this type may well ultimately lead to the development of an effective hypometabolic agent for humans. As such, it is intimately con- ned with the long term aspects of space flight.

J. Summary and Evaluation

1. Hypothermia

The advantages potentially available from hypothermia as applied to transportation and habitation in space have prompted many to consider including hypothermic techniques in such life support systems. The major fields of application would be:

1. Inclusion in primary life support systems to decrease logistic requirements of prolonged space flights.
2. Inclusion in life support systems to utilize the protective benefits offered.
3. Inclusion as a back-up in life support systems for either of the above purposes.
4. Inclusion in space medical-surgical modules.

In addition, advances in terrestrial applications of hypothermia as fall-out from space oriented research and development is to be considered in evaluating the advisability of vigorously pursuing such space oriented research.

Although various limited applications of hypothermia have been recognized and used for many centuries, only during the past two decades has this technique been refined and extensively applied to make fuller use of its potential value. The major stimulus to these modern advances has been to extend cardiac and great vessel surgical capabilities. It is important to realize that many potential applications have not been thoroughly investigated simply because the need did not previously exist.

It is clear that induced hypothermia in homeothermic animals, specifically man, is not at all comparable to normal hibernation in hibernating animals. Tremendous reduction of human metabolic requirements is feasible with the use of profound hypothermia. However, under such conditions, survival of the subject at this time is entirely dependent upon continuous and close control of his major physiologic systems by complex equipment in the hands of a highly trained team.

The weight and cube characteristics of present equipment far exceed the limitations of space logistics. However, Drs. Ivan Brown and Wirt Smith at Duke (1963) expressed the firm belief that this equipment can be sharply reduced to very acceptable cube dimensions and to a weight of forty pounds or much less with proper intensive engineering.

In regard to attending personnel requirements, Drs. Brown and Smith are of the opinion that most of the equipment can be automated. Coupling such automated, miniaturized equipment to physiologic monitoring systems expected within the next five to ten years can foreseeably eliminate the on-board personnel requirements. The subject could initiate the required medication and connections himself, after which the process would be controlled by the automated system alone or in conjunction with monitoring terrestrial personnel.

A parallel intensive physiologic research program would be required to attain such capabilities. Particular emphasis would be placed upon prolonged and profound hypothermia, including the elimination of blood viscosity by proper blood alteration or replacement. Such a program would be specifically oriented to space requirements and would need adequate funding and staffing to permit continuous and repetitive round-the-clock experiments as are required with any sizable research program in prolonged hypothermia.

2. Other Hypometabolic Methods

The key to known and indicated advantages of hypothermia has been the production of a state of marked hypometabolism. With hypothermia, this has been obtained by physical means - cold - and is the only means thus far capable of producing such low levels of metabolism in man. The method entails complex equipment and surgical procedures.

Another approach is to use pharmaceutical rather than physical means. The technical advantages of the latter method are clear, since the mechanical, surgical, and personnel requirement problems would be bypassed.

With his comparatively crude methods, man is attempting to imitate the natural hibernation of hibernating animals. More knowledge is being gained of the details of physiologic structure and function which occur during this latter process. The temperature coefficient and energy level characteristics of hibernating enzyme and other systems are entirely different from those of man. Similar differences appear to exist in estivating animals.

Although grave doubt exists as to the feasibility of duplicating all these processes in man, it is reasonable to expect that identification of specific agents involved can result in a true breakthrough in the effort to develop an effective hypometabolic agent for humans.

K. Conclusions

1. Man's metabolic requirements can be significantly reduced by prolon-prolonged periods of hypometabolism.

2. Significant added protection for humans against radiation, g forces, and bacteriologic and viral infections is indicated by the use of induced hypometabolism.

3. Hypothermia is the only currently available means capable of producing the required degree of hypometabolism.

4. Refinement of the techniques and equipment in conjunction with accelerated basic and applied research in hypothermia can be expected to result in an acceptable hypothermic system for space travel and habitation within five to fifteen years.

5. Accentuation of basic research in the biochemical control of metabolism, in both man and other animal species, is strongly indicated to develop an effective pharmaceutical hypometabolic agent.

6. Definite terrestrial medical-surgical fall-out will result from the foregoing programs.

The majority of the beneficial effects of hypothermia are essentially the result of reduced oxygen and other nutritional requirements resulting from the hypometabolic state. The advantages of this state of reduced metabolism are quite impressive under certain circumstances and the potential space application in regard to life support systems and extraterrestrial medical therapy. The elements of added physiological protection and reduced physiological needs are powerful arguments, indeed. We must provide as much secondary backup to the astronaut as is practical, in addition to supplying his primary line of life support. This would be more applicable to the longer missions which would entail significantly extended periods during which the physical and mental abilities of one or more of the crew would not be required.

Even more significant, perhaps, would be the inclusion of hypometabolic capabilities in an emergency life support system for even the shorter flights, to be available in the event of vehicle control or other failure. Under such circumstances, the additional mission time could create demands far exceeding the capabilities of onboard supplies if such were used at normo-metabolic rates. Continued research in hypometabolism could achieve this purpose.

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IV. DRUGS

A. Introduction

In the not too distant future, space flights of from a few months to several years will be a reality. Advanced planning and research efforts, therefore, must be directed to include means of reducing the almost prohibitive size and weight requirements of the life support systems. Accordingly, consideration must be given to the possibility of obtaining a precise pharmacological control over many physiologic and psychologic functions in an effort to control man's limitations and augment his capabilities in an effort to drastically reduce the life support systems requirement. Certain specifics are under consideration and are discussed in detail below.

B. Anxiety and Depression

The relief of anxiety and/or depression has occupied the efforts of many people in the last few years.

The narcotic analgesics (morphine and its congeners) have considerable ability to abolish anxiety, and the major tranquilizers (phenothiazines) are also helpful in a different sort of way.

However, in stable individuals some anxiety appears to be a necessary adjunct to judgment and such individuals often function most effectively under the influence of some psychological stress. There is no drug whose sole action is just to make an individual less anxious. In a difficult situation, it might be preferable to be cold sober. During certain periods of inactivity, however, one might wish to temporarily reduce anxiety and in this case perhaps the use of tranquilizers would be most effective with the least interference with efficiency. All the narcotic analgesics (morphine, etc.) have quite undesirable effects in that they can very adversely reduce a man's concern for his fellow man with disasterous consequences. They also have other serious disadvantagous side effects.

Depression can be alleviated by the so-called "amine oxidase inhibitors" but they seem to be most effective in cases where the cause of the depression is within the individual. The best safeguard to depression is a healthy individual psychological resiliance. The "amine oxidase" inhibitors might be effective in counteracting depression associated with prolonged isolation, but measures such as constant communication would be more effective against the depressing effect of isolation.

Agression may be decreased by tranquilizers and possibly increased by sex hormones.

Table IV-I, taken from Medical Research Digest (1962), includes tranquilizers and antidepressants which have been reported to have some degree of efficacy. Presumably the tranquilizer symptoms are not always separate entities, nor are drug effects always clear-cut. The frequency and types of side effects have not been considered. An attempt to select from this list drugs which might be suitable for use in long space flights would necessitate a detailed understanding of the desired and undesired effects as well as a thorough evaluation of all activities of each drug.

Code: X = Use supported by at least one controlled study.

Y = Reported in literature or in manufacturer's brochure.

? = Efficacy questioned by at least one controlled study; or usefulness only equivocally supported by uncontrolled studies.

Xenon, the rare gas, is known to have depressant actions on the nervous system. In some ways, it is an ideal anesthetic gas, but is not used for this purpose because of its great expense.

Recently (Science, 1962) it has been shown that Xenon can be reacted to form salts. This opens up many possibilities for the study of the actions of Xenon compounds. It is anticipated that such compounds should have a unique CNS depressant action which may be quite different from any known drugs and may also prove non-toxic. Xenon compounds may be used then to produce a simulated state of human hibernation.

C. Fatigue

The problem of listing drugs for the relief or prevention of fatigue is immediately compounded by a question of definition of fatigue. In a lengthy review Bartley (1957) pointed out the inadequacies of the old definitions of fatigue which were:

(1) objective fatigue = work decrement
(2) subjective fatigue = man's self-appraisal in terms of feeling
(3) physiological fatigue = changes in activity of body mechanisms

Bartley preferred to consider fatigue a matter of disorganization, not necessarily involving impairment, which can occur at a number of levels. His review was divided into sections which relate to these levels of activity:

(1) cellular activity and dysfunction
(2) fatigue related to failure or change in function of a tissue system
(3) fatigue of the whole organism considered as a lack of energy
(4) fatigue as disorganization of function rather than energy lack

The problem might be considered a matter of semantics except that definition is essential to the devising of proper test methods.

TABLE IV-I

TRANQUILIZERS AND ANTIDEPRESSANTS

TRANQUILIZERS	USES	
	Psychoses	Neuroses
Phenothiazine Derivatives		
Dimethylamine Series		
chlorpromazine (Thorazine)	X	Y
methoxypromazine (Tentone)	?	?
promazine (Sparine)	?	Y
promethazine (Phenegran)	-	Y
propiomazine (Largon)	-	Y
triflupromazine (Vesprin)	X	Y
trimeprazine (Temaril)	-	Y
Piperazine Series		
acetophenazine (Tindal)	Y	Y
fluphenazine (Permitil, Prolixin)	X	Y
perphenazine (Trilafon)	X	Y
prochlorperazine (Compazine)	X	X
thiopropazate (Dartal)	X	Y
trifluoperazine (Stelazine)	X	-
Piperidine Series		
mepazine (Pacatal)	?	Y
thioridazine (Mellaril)	X	X
Rauwolfia Alkaloids		
alseroxylon	Y	Y
deserpidine (Harmonyl)	X	Y
rescinnamine (Moderil)	Y	Y
reserpine	X	Y
Substituted Diols		
emylcamate (Striatran)	-	Y
meprobamate (Equanil)	-	X
phenagylcodol (Ultran)	-	Y

TABLE IV-I (continued)

Compounds of Miscellaneous Structure		
azacyclonal (Frenquel)	?	-
benactyzine (Suavitil)	-	?
buclizine (Softran)	-	Y
captodiamine (Suvren)	-	Y
chlordiazepoxide (Librium)	Y	X
ectylurea (Levanil, Nostyn)	-	Y
etchlorvynol (Placidyl)	-	Y
hydroxyzine (Atrax, Vistaril)	-	Y
mephenoxalone (Trepidone)	-	Y
oxanamide (Quiactin)	-	Y
promoxolane (Dimethylane)	-	Y

ANTIDEPRESSANTS*	Depression
MAO Inhibitors - Hydrazines	
isocarboxazid (Marplan)	X
nialamide (Niamid)	X
phenelzine (Nardil)	X
MAO Inhibitors - Nonhydrazines	
etryptamine (Monase)	Y
tranylcypromine (Parnate)	Y
Amphetamines	
amphetamine (Benzedrine)	Y
d-amphetamine (Dexedrine)	Y
methamphetamine	Y
Iminodibenzyl Derivatives	
amitriptyline (Elavil)	X
imipramine (Tolfranil)	X
Compounds of Miscellaneous Structure	
deanol (Deaner)	?
methylphenidate (Ritalin)	?
phenmetrazine (Preludin)	Y
pipradrol (Meratran)	Y
Combination	
Benactyzine and meprobamate (Deprol	X

* No attempt has been made to distinguish between neurotic and psychotic depression.

The most frequently used tests have involved some mental effort (simple addition or subtraction, for example) over varying periods of time in normal or sleep-deprived subjects. In general, CNS stimulants, particularly the amphetamines, have been studied. The duration of antifatigue effect is limited to perhaps intermittent use for say 72 hours. If provision is not made for sleep and the drug continued, the individual may suddenly without warning fall into a deep sleep or may hallucinate.

As long ago as 1938 Barmack reported that 10 mg. of 'Benzedrine' improved the subjective feelings of subjects and increased the number of arithmetic problems attempted during a two hour period. Korentsky et al (1959) reported that dextroamphetamine improved performance of sleep-deprived subjects in some psychological tests but returned only the least impaired performances to the non-sleep deprived level. Holliday and Devery (1962) tested several drugs in sleep-deprived healthy subjects doing addition and subtraction of numbers. Two stimulants, dextro-amphetamine and an experimental drug W1206, significantly enhanced performance beyond that of subjects who received meprobamate, amitriptyline, or placebo. The work of the group who received amitriptyline was significantly retarded. Improved performance in a different type of test was reported by Eysenck, et al (1957). Their subjects were required to follow closely a small metal disc on a turntable. Performance was improved with dextro-amphetamine, while subjects who had received sodium amytal were less productive than those who received placebos.

A different approach and a different type of compound has recently been studied by Shaw et al (1962). The material tested was a mixture of potassium and magnesium salts of aspartic acid (Spartase, Wyeth). The use of Spartase in treatment of fatigue was based on its ability to delay exhaustion in swimming rats. It has been hypothesized that the aspartates delay fatigue by delaying "metabolic exhaustion" which has been attributed to exhaustion of one or more substrates required by the Krebs cycle. Shaw et al demonstrated relief of fatigue by Spartase in double blind trials in patients complaining of chronic fatigue with or without organic disease.

D. Protection Against Acceleration

Very little has been published on protection by drugs against acceleration stresses; it is assumed that compounds are being tested for such activity, but for proprietary reasons are not yet available. However, Browne and Polis have pointed out the involvement of endocrine systems in withstanding acceleration stress.

Browne (1959) showed that insulin-induced hypoglycemia reduces resistance to gravity. Polis (1961) reported that the survival time of rats exposed to 20G was significantly increased by hypophysectomy and significantly decreased by adrenalectomy. Sanco and Meineri (1961) prolonged the resistance of rabbits to 3G by parenteral administration of either epinephrine or nor-epinephrine. In his most recent paper Polis (1962) indicates that a number of agents have been tried. He states that tranquilizer and anti-adrenergic compounds were at best inactive and usually harmful. Only marginal-effects were seen with a psychic energizer and a steroid inhibitor. Polis did, however, find that Lucidril (2-dimethylaminoethyl p-chlorophenoxyacetate) significantly increased the tolerance of rats to acceleration at 20G. The effect was dose-related, lasted only about four hours, and required several days of treatment before becoming apparent. He suggested that the effect might be mediated via the hypothalamus, an hypothesis which can be tied in with his earlier findings in hypophysectomized rats.

E. Protection Against Heat Stress

In the last 10 years, there has been very little information on protection of either animals or man against extremes of heat. There have also been a number of studies on physical means of protection from the physiological effects of extremes, but drugs have received little attention.

Protection against one or more effects of heat stress has been obtained with chlorpromazine, reserpine, ascorbic acid, methimazole, Pendiomide, cortisone, and vitamin E. In 1958 DeBias et al tested a series of agents with effects on the autonomic nervous system in adrenalectomized male rats exposed to temperatures of 37.5°C for six hours. Chlorpromazine administered intramuscularly at 10mg./kg. significantly increased survival of the rats; this effect was enhanced by the addition of sub-effective doses of hydrocortisone. Pendiomide, a ganglion blocker, was ineffective at an intramuscular dose of 0.7 mg./kg. but when subeffective doses of hydrocortisone were added the survival rate was significantly increased. Dibenamine and phentolamine hydrochloride which are adrenolytic agents and propantheline bromide, an anti-cholinergic, decreased the rate of survival of heated adrenalectomized rats. It was postulated that the effect of chlorpromazine was not due to its hypothermic activity since the colon temperatures of the treated and untreated rats did not differ.

Juskiewicz (1961) confirmed the protective effects of chlorpromazine in intact rats. He injected 5 mg./kg. or 20 mg./kg. intramuscularly one hour before exposing rats to 43°C. Chlorpromazine also decreased the rate of depletion of adrenal ascorbic acid and the rate of increase of adrenal gland weight in the exposed rats. Similar but not statistically significant results were obtained with reserpine 10 mcg./kg. or 20 mcg./kg. given one hour before exposure or with two 100 mg./kg. doses of ascorbic acid injected at 24 hours and one hour before exposure. The protection effects of chlorpromazine and ascorbic acid against heat stress were enhanced by concomitant administration of the two agents. Juskiewicz and Jones (1961) further found that an intramuscular injection of 3 mg./kg. of chlorpromazine protected pigs exposed to 40°C. There was a statistically significant increase in survival and a significant decrease in the depletion of adrenal ascorbic acid and in body weight loss.

In a study of the relation of thyroid activity to stress Juskiewicz found that methimazole, a thyroid antagonist, administered at a daily dose of 6 mg./kg. for five days before exposure to heat increased the survival time of rats and decreased the rate of depletion of adrenal ascorbic acid.

A publication on heat stress, Wiswell (1961), reported that vitamin E (oc-tocopherol) exerted a protective effect in rabbits exposed to 45°C for 60, 75, or 90 minutes or 50°C for 60 minutes. Vitamin E was administered orally at a daily dose of 20 mg. for fourteen days before exposure to heat. All treated animals showed less change in rectal temperature and less weight loss than untreated animals during exposure to heat. The protective effect was greatest in rabbits exposed to 45°C for 75 minutes.

This intriguing information indicates the possibility of providing protection against heat stress by pharmacological means. It is, however, obvious that much work will be necessary to determine the most effective agents and the mechanisms involved.

F. Agents Affecting Metabolism (See also Hypothermia)

Metabolism is lowest at rest and during sleep. The only effective drugs for this are the antithyroid drugs. They produce a sluggish individual whose responsiveness and alertness is decreased. The maximal effect is small. If the sequence of events leading to metabolite production is blocked, the substance just prior to the block will accumulate. All events leading to such a situation produce coma.

In healthy adults the heart rate is rather labile and decreasing it does not reduce metabolism. The normal body resists blood pressure changes especially a reduction so vigorously that it is extremely difficult to achieve and will undoubtedly result in the disablement of the individual.

The CO_2 carrying capacity of the erythrocytes can be reduced with diamox (carbonic anhydrase inhibitors). This may cause headache and malaise but at rest there is not much disablement. However this results in no useful reduction in metabolism. The CO_2 accumulates a little but still is removed.

True hibernation is unknown in man. After the thermotoxic center of the hypothalamus is knocked out with the general anaesthetic drugs of the chlorpromazine type (phenothiazines), a fall in body temperature will result, but ventricular fibrillation may occur if temperature falls too much. Some of the glycerol ethers caused a fall of temperature in guinea pigs but not in dogs.

In the clinical publications the emphasis is on the use of induced hypothermia during surgery or as a therapeutic measure. Many studies of hypothermia have been devoted to its physiological and metabolic effects. The techniques of induction of hypothermia in most common use are physical as, for example, surface cooling by packing in ice, etc., or extracorporeal cooling of the blood.

The role of drugs in this process is a minor one; some space in reviews and other publications has been devoted to discussions of the most suitable anesthetics. With regard to drugs such as chlorpromazine or the "lytic cocktail" (chlorpromazine, promethazine, and meperidine) the comments of R.D. Dripps in the publication of the National Academy of Sciences are significant: neither chlorpromazine, promethazine, meperidine or Hydergine, alone or in combination has produced a significant lowering of body temperature without added cold. Some or all of them may be valuable adjuncts to cooling but none can serve as the primary agent.

G. Motion Sickness

The listing of antimotion sickness agents according to prophylactic effectiveness by Moyer (1957) gives a good picture of the present situation. The highest protection against airsickness is afforded by scopolamine, 1.0 and 0.65 mg., followed fairly closely by Marezine, 50 mg., then by Benadryl, 50 mg. In third place are Bonamine, 50 mg., Phenergan, 25 mg., and Trimeton, 50 mg., while Dramamine, 100 mg., follows closely as fourth. The order of prophylactic efficacy in seasickness is: first: Bonamine, 50 mg. (once daily); second: Phenergan, 25 mg., (twice daily); third: Marezine, 50 mg.; fourth: Benadryl, 50 mg., and Dramamine, 100 mg.; fifth: Trimeton, 25 mg., and last: scopolamine, 0.5 mg.

A review of pertinent studies which form the background for these conclusions follows:

1. Belladonna Alkaloids

Since many of the symptoms of motion sickness resemble those produced by stimulation of the parasympathetic system, parasympatholytic drugs were the first tried. For almost 60 years the belladonna alkaloids, atropine, hyoscine and hyoscyamine remained the only effective agents available against motion sickness. The most widely used and studied has been 1-hyoscine (scopolamine). There is no proof that hyoscine is superior to atropine or hyoscyamine but it is generally believed to produce fewer side effects (Smith, 1948). As scopolamine is an effective prophylactic against air, sea and swing sickness in man, it has been adopted as a standard for the comparison of new or potentially effective drugs. The dose generally used is 0.65-0.75 mg. Glaser (1951) used 1.0 mg. of scopolamine hydrobromide and found it significantly superior to Phenergan, 25 mg., and Benadryl, 25 mg. in preventing seasickness. With the same dose of scopolamine Chinn and Milch (1953) demonstrated a similar high degree of protecting against airsickness. In his 1957 report on effective antiemetic agents, Moyer states that scopolamine is the most potent drug against airsickness when used in single doses but adds that it is not the agent of choice because of its side effects. The literature of the early forties contains numerous references to various mixtures of belladonna alkaloids and combinations with thiobarbiturate, amytal, etc. (Fields, 1943). Although each of these mixtures afforded good protection, there was no evidence that any of them were superior to scopolamine alone.

2. Synthetic Antispasmodics

Trials with synthetic substitutes for belladonna alkaloids (Chinn, 1953) such as Banthine (methantholine), Bentyl (dicyclomine hydrochloride) and Buscopan (hyoscine-N-bromobutylate) showed that none was able to prevent motion sickness. These findings suggest that there is no relation between antispasmodic activity and efficacy in motion sickness.

3. Amphetamine Sulfate and d-Amphetamine

Blackham (1939) listed amphetamine sulfate with bromides, cocaine, and chloral hydrate as the best remedies against seasickness. Hill (1937), who treated 100 cases of seasickness with 'Benzedrine', found improvement in 39% of the subjects and stated that the drug might be of value in cases of excessive vagus activity.

D-amphetamine has also been tried in various mixtures; the most recent report on a combination containing dexamphetamine, scopolamine bromohydrate and bellafolin was made by Monnier (1955). At first injected the mixture was later administered in the form of suppositories which proved to be more convenient and as effective as the parenteral route. Of the 324 trans-atlantic passengers treated with two suppositories daily of this mixture, 241 and 78 experienced full and partial relief respectively. The exact dosage was not given.

4. Pyridoxine

Pyridoxine, which has been frequently used alone or in combination to counteract emesis of different etiology, was also tested against motion sickness. Thuer (1952) found it ineffective, while Benkendorf (1953), who administered 50 mg. of pyridoxine to a large series of seasick patients, reported good results. Ninety per cent of 2500 patients receiving pyridoxine suppositories experienced improvement while 90 patients given placebo suppositories were not improved.

5. Antihistamines

In 1949 Gay and Carlinger reported on the striking effectiveness of Dramamine in preventing seasickness during a rough North Atlantic crossing. One hundred thirty-four soldiers who received 100 mg. of Dramamine upon embarkation and 400 mg. daily in divided doses for at least 48 hours remained completely protected. The therapeutic effect of the drug was equally impressive: complete relief was observed within 20-60 minutes in 372 (95.6%) of 389 men who became seasick. Administration of placebo to 50 seasick subjects resulted in 38 failures (64.4%). Although the execution of the experiment was criticized by Tyler and Bard (1949) on the basis of uneven distribution of Dramamine and placebo treatment and the failure to include a known prophylactic, the effectiveness of Dramamine was repeatedly and consistently confirmed by other investigators.

Strickland and Hahn (1949) reported that the drug also affords significant protection from airsickness, but could detect no difference between Dramamine and placebo in protecting against swing sickness (Strickland, 1950). When the same authors compared 100 mg. of Dramamine with 0.65 mg. of hyoscine, given one hour prior to flight, airsickness occurred in 33% of the subjects on Dramamine and only in 20.4% of the persons on hyoscine. This finding that Dramamine is not superior to hyoscine against airsickness was confirmed subsequently by other investigators and further studies showed that there was no significant difference between the ability of Dramamine and that of hyoscine to protect from seasickness (1950).

Since Dramamine is the 8-chlorotheophylline salt of dimethylaminoethylbenzohydryl ether and Benadryl is the hydrochloride of the same base, it was obvious to expect that Benadryl would display very similar behavior. Chen and Ensor (1950) pointed out that 8-chlorotheophylline, unlike theophylline, is not a pharmacological agent, as it produces no demonstrable effect on cardiac output, renal excretion and central nervous system. In their experiments on dogs 20 mg. of 8-chlorotheophylline were ineffective and displayed no apomorphine antagonism while 20 mg. of Benadryl and 20 mg. of Dramamine showed equal anti-apomorphine potency. Schwab (1952) stated that both Dramamine and Benadryl have almost identical effects after absorption into the body and thus 50 mg. of Dramamine (due to weight ratio of diphenhydramine hydrochloride and 8-chlorotheophylline) act like 37 mg. of Benadryl. This author goes even further ascribing the popularity of Dramamine over that of Benadryl to the tablet strength: Benadryl is supplied only as 25 and 50 mg. tablets which at the ratio given above would make the 25 mg. strength too weak and the 50 mg. strength too potent as compared with the 50 mg. tablet strength of Dramamine. However, Gutner, Gould and Batterman (1951) in their comparative experiments on the effect on vestibular function of Dramamine 100 mg., Benadryl 50 mg., 8-chlorotheophylline 100 mg., aminophylline 500 mg., Scopolamine 0.6 mg. and seconal sodium 100 mg., found that Dramamine indeed behaves differently from Benadryl. The tests used as criteria were the galvanic stimulation of the mastoid area, and the microcaloric method involving the production of a nystagmus by 2 cc of ice water and measurement of this reaction in terms of onset and duration. Tested in 13 subjects Dramamine consistently depressed the vestibular function: the time of onset was prolonged by 63% and the duration of the nystagmus was shortened by 50%. Similar results were seen with galvanic stimulation. Benadryl, aminophylline, 8-chlorotheophylline and secobarbital sodium produced no significant alterations. Scopolamine unexpectedly prolonged the duration of nystagmus in 4/5 subjects by 23%. Although of interest, the interpretation of these findings is difficult as both Benadryl and scopolamine are effective antiemetic agents beyond any doubt.

A number of additional studies have consistently confirmed the reliable protection afforded by Benadryl. Chinn and Handford (1953) tested a number of drugs aboard navy transports for their ability to protect against seasickness. 50 mg. of Benadryl 3 times daily was found to display significant protection along with various other drugs (Trimeton, Trimeton-scopolamine mixture, Postafene and Phenergan, etc.). However, 50 mg. of Dramamine 3 times daily gave no protection. Only slight side effects were reported for all drugs under study.

The protective properties of Dramamine and Benadryl stimulated considerable speculation for they suggested that antimotion sickness efficacy might be connected to antihistamine potency. This hypothesis was soon disproven by the demonstration that many powerful antihistamines failed to protect from motion sickness. Other antihistamines, however, have been found to possess anti-motion sickness efficacy: the diethyl analogue of Benadryl, β(diethylaminoethylbenhydrylether), is among the compounds displaying significant protection against seasickness in the study quoted before (Chinn and Handford). Trimeton maleate indicated promising protection against airsickness. This was confirmed in more extensive studies not only for airsickness, but for seasickness as well.

An important group of antihistamines introduced in the early fifties includes several members of the piperazine series which display marked anti-motion sickness efficacy. The most potent and the most widely used of these at the present time is Bonamine (meclisine) which at a dose of 50 mg. once daily protects against seasickness.

With more and more compounds added to the list of antimotion sickness remedies a joint Army-Navy-Air Force project for large scale screening of preparations was undertaken (Handford, 1954), primarily to re-evaluate Benadryl and scopolamine and to determine the comparative efficacy of Bonamine. The object of the trial was to find the drug of choice and to establish the optimum dosage schedule required to produce maximal protection and minimal side effects. Under the conditions of the experiment, 50 mg. of Benadryl given t.i.d. and a single dose of 50 mg. of Bonamine given at the time of sailing afforded significant protection at less than the 0.01 level of probability with few untoward side effects. 1 mg. of scopolamine b.i.d. provided no protection and produced a number of unpleasant side effects. Chlorpromazine tested for the first time at sea gave no significant protection. These experiments reconfirmed the prolonged duration of action of a single 50 mg. dose of Bonamine which had been reported in the previous study by Chinn (1953).

Three years later the Army, Navy, Air Force motion sickness team published a new report (1956) on trials with 26 drugs in 16,920 soldiers during 15 transatlantic crossings. Significant protection was afforded by the following drugs:

50 mg. of Bonamine once or three times daily
50 mg. of Marezine twice and three times daily
25 mg. of Phenergan twice and three times daily
50 mg. of Vibazine three times daily
100 mg. of Dramamine three times daily
1 mg. of Cogentin three times daily
50 mg. of Benadryl three times daily
50 mg. of Sandostene three times daily
50 mg. of Trimeton three times daily

Of the effective agents Bonamine, Marezine and Phenergan were significantly more effective than the other drugs. Not all drugs were equally effective at all times; sometimes there was no appreciable difference between placebo and an otherwise effective drug (for instance Benadryl, Marezine) while other compounds which were eventually proven to be ineffective gave occasional protection (pyridoxine, thiamine).

Compounds proven ineffective included hyoscine, scopolamine methobromide, racemic calcium pantothenate, thiamine, pyridoxine, reserpine, and 'Thorazine' among other phenothiazine derivatives. The failure of the latter two to afford protection provides indirect evidence on the minor role of psychic factors in seasickness. If fear, apprehension or anxiety were conducive to the onset of motion sickness, these drugs could have been expected to reduce the incidence of motion sickness. Except for drowsiness observed after benztropine and promethazine, the effective agents produced few side effects. In the ineffective groups the highest incidence of drowsiness was seen with scopolamine hydrobromide and the Rauwolfia alkaloids.

The latest report on large scale testing of antimotion sickness drugs in military personnel on transport ships was made by Trumbull and Chinn (1960). This study was undertaken to serve a dual purpose: comparative screening of new compounds and elucidation of the mechanism by which drugs protect against motion sickness. Representatives of several pharmacological categories were tested: (a) parasympatholytic-antiparkinson agents, like atropine, phenglutarimide (Aturban) orphenadrine (Disipal);(b) antihistamines like cyclizine (Marezine), meclizine (Bonamine), and the closely related cinnarazine (Mitronal);(c) MAO inhibitors to elucidate whether or not motion sickness was associated with accumulation of naturally occurring amines. Tested on three different trips the drugs were given three times a day, nine capsules altogether. On the first trip only Bonamine, 50 mg., and phenglutarimide, 2.5 mg., were effective. On the second trip Bonamine 50 mg. was highly effective while Mitronal, 7.5 mg., provided some protection. On the third trip, Marezine, 50 mg., was highly effective and prevented vomiting in all subjects. Atropine and orphenadrine showed some, although not statistically significant, activity. The MAO inhibitors tested behaved like the placebos, thus disproving the hypothesis that vomiting of motion sickness may be a consequence of biogenic amines.

H. Conclusions

The foregoing section has covered those pharmacologic agents which it is felt could have a significant effect on augmenting man's performance while undergoing the stresses of space flight and extraterrestrial exploration. The areas of anxiety and depression, fatigue, acceleroprotective, thermo-protective, metabolic reducing agents, and motion sickness preventatives were discussed in detail. No unnecessary stress should be placed on the method of administration discussed, as it is foreseen that varied routes may be available for these agents. The area of radiation protection has intentionally been ignored because of the profuse quantity of material available on this topic. The pharmacoradio-protective agents useful in man space probes have been covered in detail in the Armed Forces Technical Report #AD277689, prepared by the School of Aviation, Madison, Brooks Air Force Base, 1962, and for this reason they were omitted from consideration in this report.

The ability to attain a state of pharmacologic control over the psycho-physiologic function of space pilots, is an intriguing concept and is definitely worthy of active research efforts. Therefore, we would like to recommend that a central store of information on the pharmacologic action of chemicals and other substances, which would be useful for the control and modification of human physiology in space, be initiated. We believe that a feasibility study on a modest scale would be well worthwhile. Initially, it might well be fruitful to consider techniques for the integration of the several large private collections that now exist in various centers.

In the gathering of data on pharmacologic agents, we found a great deal of resistance from the major drug houses to release any information. In this connection also there is a concentrated effort by such institutions to develop drugs which were function-specific against a known or suspected psychophysiologic deviations. What is proposed, however, is a central source of readily available information on all of the effects of such agents and not just those produced for their therapeutic efficacy. This information center would instantly be able to specify any agent or combination which might attain a desired effect, in a research project which may not be in the principal area of pharmacotherapeutics.

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V. SENSORY DEPRIVATION

A. Hypodynamic Effects of Long-Term Space Missions

It will be recalled that the major purpose of the present study is the identification and evaluation of the means by which man can be prepared to cope successfully with the many stresses which may affect him during long-term space missions. The need for this study arises because man is basically a biological organism designed to operate within the parameters defined by the earth environment. Despite a remarkable degree of "over-design," there are many areas in which man's capabilities fall short of the requirements posed by such missions. Consequently, important segments of the present effort are devoted to the analysis of those physiological systems such as the cardiovascular, pulmonary, and endocrine which are of principal concern during such missions and to the investigation of the methods by which their capabilities can be extended, their limitations circumvented.

Recently, much attention has become focused on the fact that some of the conditions which may be presumed to arise during long-term space excursions are powerful psychological stressors (cf. Solomon et al, 1957; Wheaton, 1959). The evidence, which will be reviewed in detail below, shows that the economy of man's psychological resources has definite limitations which can be exceeded by many seemingly innocuous factors. This is an important problem area since the effectiveness of man is a function of his psychological as well as physiological integrity. The success of a mission, and perhaps the life of the individual astronaut, will depend heavily upon the psychological well-being of every crew member. The study of psychological stressors and the means by which they can be minimized or controlled therefore fall within the meaning of the Cyborg concept.

A consideration of the psychological aspects of long-term space flight reveals a number of complex problem areas (cf. Chambers, 1962). Many of these have been studied in earth-bound simulators. The experience of crews of submarines is also instructive in many areas. A few of the anticipated problems may be mentioned for illustrative purposes.

1. Disruption of the normal 24 hour sleep-waking cycle is highly probable, necessitating the study of optimum work-rest cycles (cf. Adams & Chiles, 1960, 1961; Chiles & Adams, 1961).

2. The weightless environment *per se* may have some deleterious effects on psychomotor performance, although the indications are that these can be overcome to significant degrees by proper training (see Loftus & Hammer, 1961, for a review; Chambers, 1962).

3. Work proficiency in a small sealed cabin can be maintained at relatively high levels for extended periods of time, e.g., 30 days, by experienced pilots, provided work-rest cycles and task parameters are optimal; inexperienced subjects tend to deteriorate at lower stress levels (Hauty, 1959, 1960; Hauty & Payne, 1958; Hartman, 1961; Hartman, McKenzie & Welch, 1962; McKenzie, Hartman & Welch, 1961).

The specific problem to be analyzed here is the reported development of such phenomena as perceptual disturbances, hallucinations and other visual images, or cognitive difficulties, as results of prolonged exposure to a hypodynamic environment (cf. Heron, Bexton, Hebb, 1953; Bexton, Heron & Scott, 1954; Heron, Doane & Scott, 1956). Because more than the manipulation of sensory stimuli is involved, the term "hypodynamic" is used here, instead of "sensory deprivation," "perceptual isolation," "isolation," and the like, which seem to have a more restricted meaning. The conditions in the laboratory and those anticipated in an actual space capsule are similar in many respects, as may be seen from a consideration of Table V-1.

TABLE V-1

A COMPARISON OF THE FACTORS OPERATIVE IN LABORATORY HYPODYNAMIC EXPERIMENTS AND IN A HYPOTHETICAL SPACE CAPSULE

Variable	Laboratory	Space Capsule
1. Number of subjects	One	Two or more
2. Confinement volume	Extremely limited	Relatively large
3. Motor activity	Extremely limited	Relatively unrestricted
4. Social isolation		
a. from other individuals	Extreme	Minimal
b. from society as a whole	Extreme	Extreme
5. Intensity of sensory stimuli	Greatly reduced	Somewhat reduced
6. Patterning of sensory stimuli	Greatly limited	Somewhat limited
7. Variety of sensory stimuli	Greatly reduced	Reduced
8. Communication:		
a. intensiveness	Extremely limited	Unlimited
b. extent	Extremely limited	Limited
9. Typical exposure period	Several days	Several months

As this table shows, the differences seem to be a matter of degree. This suggests that the occurrence of hypodynamic effects on a space mission is a possibility. If so, the resulting behavior decrements would constitute a distinct threat to the success of the mission. However, even small differences in the environmental conditions may be significant and greatly modify the variety and severity of the hypodynamic effects. For example, it appears that if relatively normal levels of perceptual activity are allowed, behavioral deterioration is minimal, even though the other factors are relatively severe (cf. Freedman, Grunebaum & Greenblatt, 1961; Wheaton, 1959). In an actual multiple-member space craft, therefore, the effects observed in the laboratory may appear to have a low probability of occurrence (Freedman & Greenblatt, 1959; Flinn, 1961; Hagen, 1961; Imus, 1961). However, the crew of a space capsule will encounter a number of stressors which do not appear in a laboratory situation (cf. Walters & Henning, 1961; Banghart & Pattishall, 1960). Among these are (1) the element of real personal danger, and (2) the effects of prolonged exposure to (a) sub- or zero-gravitational effects, (b) various types of radiation, (c) an artificial atmosphere, (d) intensive "small group" interactions, (e) a novel form of isolation from human society, and (f) the unusual visual environment of space. Such additional stressors can possible act synergistically with the hypodynamic environmental factors to produce detrimental effects on behavior, if not on 14-day flights, perhaps on 24-month missions. These considerations point to the need for a thorough re-examination of the effects of exposure to hypodynamic conditions to understand the nature of the effects, the major contributory factors, and the means by which such effects can be prevented or minimized. This latter aspect is particularly relevant for the conception of survival techniques to be instituted in the event of partial mission failures, such as loss of communications contact.

B. Psychological Responses to Environmental Stress

The experiences of shipwreck survivors (e.g., Gibson, 1953); solitary sailors (e.g., Slocum, 1900), and people isolated under polar conditions (e.g., Byrd, 1938; Ritter, 1900) demonstrate the severe psychological disturbances, including perceptual aberrations, affective changes, hallucinations, and cognitive defects, which result from prolonged exposure to such environmental conditions. It is not profitable to analyze these accounts in detail as they differ so greatly in objectivity, in the behavioral criteria used, and in other important respects. However, certain generalizations can be made. The environment in which these people find themselves is monotonous. Hour after hour, day after day, there is a sameness, a great reduction in the patterning and variety of sensory stimuli and activity. This produces a boredom of pathological dimensions. The effects of social isolation and lack of communication are usually severe, since the victims feel that they are lost. Other powerful stressors, such as danger, privation, injury and exposure, appear to act synergistically to produce the remarkable behavioral deterioration described.

Further evidence that prolonged exposure to environmental stressors of the type listed in Table V-1 can produce psychological aberrations is found in the experience of poliomyelitis patients who developed visual and auditory hallucinations after being placed in tank-type respirators. That the phenomenon is independent of the effects of disease is demonstrated by the fact that normal subjects, after several hours in the respirators, developed similar abnormalities (Mendelson & Foley, 1956). These unfortunate patients had no choice but to lie immobile in the respirator, with nothing to do but listen to the monotonous sound of the bellows, and little to look at except the ceiling. Some developed hallucinations within two hours after being placed in the respirator.

It is commonly recognized that monotony is basically the absence of interesting stimulation. This is evident even in the derivation of the term. It is therefore to be expected that stimulation reduction resulting from the loss of an important source of sensory input, such as vision or hearing, would produce similar effects. This inference is substantiated by the reports in the clinical literature of cases of "psychotic" behavioral manifestations following the loss of vision or audition (Bartlett, 1951; Greenwood, 1928; Knapp, 1948; cf. Hebb, Heath & Stuart, 1954; and Doane, Mahatoo, Heron & Scott, 1959, p. 214).

The clinical and anecdotal reports by themselves do not constitute sufficient reason to study the phenomena in the context of the space program. Such experiences are based on an unselected population, who are naive in the ways of functioning under stressful or unusual conditions, and often subjected to debilitating conditions. Of more crucial significance are data such as the occurrence of the "break-off" phenomenon (Clark & Graybiel, 1957; Ross, 1959; Simons, 1959, 1962), reported by jet pilots as an illusion of being totally separated and detached from the earth and human society. These pilots are highly qualified, well motivated individuals, experiencing none of the discomfort and frustrations found in life boats, igloos, tank respirators, or in balloon gondolas (Ross, 1959; Simons, 1959) or simulators (Beckman, Coburn, Chambers, DeForest, Augerson & Benson, 1961; Benson, Beckman, Coburn & Chambers, 1961; Chambers & Nelson, 1961; Graveline, Balke, McKenzie & Hartman, 1961; Hauty, 1959; Mitchel, 1962). Nevertheless, in one survey, 48 out of 137 pilots reported such perceptual and cognitive aberrations (Clark & Graybiel, 1957). Characteristically, break-off occurs in individuals flying routine missions alone or when direct contact with other crewmen is minimal, and at high altitudes. Under these conditions, the flyer's visual environment consists of the featureless sky, the essentially static display of the instruments and controls, and the indistinct and relatively stationary pattern of objects below. Auditory stimuli consist principally of the steady, unchanging rush of air, and his movements and internal stimuli are drastically limited by his form-fitting cockpit. Under such hypodynamic conditions, break-off sometimes occurs in as little as two hours. Break-off is abolished by increases in meaningful stimulation produced by activities such as returning to lower altitudes, joining another aircraft, or by voluntary effort to engage in some activity or problem.

Finally, it is important to realize that hallucinations and other aberrations can be induced in a normal environment when the subject is committed for a prolonged period to a rigid and extremely confining structure of stimuli. In experiments by Hauty (1959; Hauty & Payne, 1959) the subject was required to monitor complex displays for 30 consecutive hours while confined in a one-man space cabin simulator. Except for short and infrequent periods for lunch, relief, and exercise, the subjects remained at the task and were not permitted to sleep. Many complex, visual and proprioceptive hallucinations were described, such as the illusion that the meters were turning into faces, that deep holes were opening up in the floor, and feelings of floating in the air (Hauty, 1960).

1. Basic Methodology

As is well known, the initial studies on sensory deprivation were conducted in 1951 at McGill University under the direction of Prof. D. O. Hebb. The research design typical of this group comes under the category of reduction of patterned stimuli. Under the original techinque, the subjects (Ss) were confined for several days, spending their time on comfortable beds in air-conditioned cubicles which were nearly soundproof and dimly lit. The Ss wore translucent goggles which permitted maximal diffusion of light. Their hands were covered with heavy cotton gloves with cardboard "cuffs" being fitted from just below the elbow to the upper part of the hand. Cotton balls or molded ear plugs were inserted in the auditory canal so as to minimize any auditory stimulus input. Thus visual, auditory, and tactual stimulation were reduced to a very minimal level. The Ss were usually permitted some mobility since they could sit up when eating and take care of personal needs in an adjoining room. They were encouraged to communicate their thought processes which the experimenters monitored by an intercom system.

A second method, developed by Lilly (1956), had the subject suspended in a tank of water at body temperature with a pressurized black head mask. This condition reduced the intensity of physical stimuli impinging upon the subject, as well as the patterning. Under these conditions, hallucinations and other effects occurred in a shorter time, about three hours.

An analysis of the research conducted and results obtained utilizing these techniques will now be discussed.

a. Reduced Stimulus Patterning

One of the more extensive studies by the original McGill group was carried out by Bexton et al (1954). The purpose was to study the effects of a hypodynamic environment upon intellectual function during and following the isolation period, and to study the development of hallucinatory activity. A second phase dealt with isolation effects upon visual perception, tactual-form discrimination and spatial orientation.

Twenty-nine male college students were selected for the project and constituted the experimental group while twenty-seven others comprised the control group. They were asked to remain in this situation as long as possible (48-72 hours) but could terminate the experiment whenever they wished since it was assumed that some individuals would not tolerate the isolated conditions for that length of time.

The cubicles were air conditioned, semi-soundproof, and illuminated by a small bulb. An observation window was strategically placed enabling the experimenter to view and periodically record the subject's physical movements in kind and degree. The Ss lay prone on a cot, and were required to wear translucent goggles which admitted diffuse light, but prevented pattern vision. They also were required to wear heavy cotton gloves and cardboard "cuffs" which covered their forearm extending to a short distance beyond the fingers, thus minimizing tactual stimulation. A steady hum emanating from the air-conditioner motor served as a masking noise, and the walls of the cubicle prevented any discernible patterned form of auditory perception. They were permitted some mobility since they had to walk to an adjacent room for their toilet needs. In addition, they sat up on the cot to eat thus necessitating the temporary removal of the gloves and cuffs under both circumstances. An intercom between the experimenter's position and the cubicle permitted communication between the two individuals. It also served as a means of obtaining spontaneous verbalizations and "on the spot" reports of any aberrant perceptual reactions from the subject.

Intellectual functions were tested before, during and after confinement. The test given during confinement consisted of two parts. The first part included five types of mental problems taken from a number of intelligence tests. These were multiplication, arithmetic "catch" problems, completion of number series, word making and anagrams. The second part consisted of the associative learning and digit span tests taken from the Wechsler memory section. An analogies test was also included. Finally the S's susceptibility to propaganda, as affected by the sensory deprivation experience was measured. These tests were given orally, requiring the S to derive an answer solely by means of mental computation without the benefit of pencil and paper. The tests given before and after confinement were standard tests and alternate forms were employed. The tests were administered to both experimental and control groups at the same time intervals, with the control group coming to the laboratory at a scheduled time for testing under normal conditions.

The recorded propaganda text discussed arguments for and against the validity of various forms of physical phenomena, e.g. telepathy, clairvoyance, and ghosts. The Ss were given a questionnaire which measured attitudes, employing a Bogardus-type scale divided into sections corresponding to each topic of the psychical phenomena. In addition, the scale was so constructed that the S's interest level could be evaluated as well as how important he felt the topic was to him personally.

The results of the tests given during confinement demonstrated impairment on test in the series. A comparison of the error scores and the number of requests to repeat the problem indicates that during isolation, the experimental group was definitely inferior to the control. However, significant differences were only on word making and number series. In the second part there were no significant differences between the two groups on the digit span and analogies test. On the whole, therefore, there was a consistently inferior performance on the part of the experimental group compared to the control group for performance tasks on the test battery.

The test results of the two groups on the post-confinement battery demonstrated significantly inferior performance on the part of the experimental group in the Kohs Blocks, Digit Symbol, Thurstone-Gottschaldt Figure, Copy Passage, Delta Blocks, and Picture Anomaly. There was no significant difference in the case of mirror tracing. The questionnaire measuring the effectiveness of propaganda showed that the experimental group was significantly more susceptible than the control group.

Hallucinatory experience was defined as a spontaneous "perception without object." Three subjects experienced hallucinations. The remaining Ss reported some form of visual imagery, from simple (dots, lines) to complex (actual scenes), which could be subjected to examination. An attempt was made to determine whether or not diffuse light induced hallucinatory effects. Opaque goggles were placed on three Ss who had been in isolation for several days and were reporting that persistent hallucinations temporarily became more vivid; approximately two hours later, the effects had disappeared in the case of two subjects and diminished considerably for the third.

The second phase of the experiment was to study the effects of prolonged isolation upon visual perception, tactual-form discrimination and spatial orientation. The experimental conditions were similar to the first phase previously described. Twelve Ss were employed as the experimental group whereas twenty others comprised the control group. The duration of isolation was ninety-six hours. A battery of perceptual tests was given on the day prior to the actual isolation period. EEG records were taken prior to the confinement and taken twice daily during confinement on a pre-determined time schedule, as well as when the S was having hallucinatory experiences or when he was conversing. Tests on tactual form discrimination and spatial orientation were given prior to entering the cubicle as well as at the forty-eight and seventy-two hour points during isolation.

The Ss all reported visual disturbances upon removing the goggles with most effects disappearing within several minutes. In a few cases the effects persisted for several hours. The distrubances were described as follows:

(a) Movement of objects, lines, room walls, etc. contracting and expanding in rhythmic sequences.

(b) Objects changing size and shape.

(c) Surfaces shimmering, undulating, swirling, warping and curving.

(d) Swelling of lines or plane surfaces. When asked to touch the point of fixation, the S usually was short or overshot the mark.

(e) Downward curving of the ends of horizontal lines if viewed above a horizontal plane.

(f) Parallel lines seem to be displaced near the fixation point, producing a barrel shaped figure.

(g) Movement of S's head position was followed by a corresponding movement of the objects in his visual field.

(h) Marked positive and negative after-images.

(i) Increments in color intensity, saturation, and color contrasts.

It was emphasized that these effects were observed both monocularly and binocularly.

The effect of isolation on tactual perception was demonstrated by means of a tambour system attached to the cot. Although the movements were sporadic, there was a progressive increase in movement, indicating a general state of increased restlessness. The data on motor movement gives some indication of the sleep-waking cycle. It was found that Ss slept less during the final phase of the project than during the initial phase.

Doane et al (1959), also in the McGill group, employed essentially the same method in a further investigation of the perceptual effects of prolonged isolation. The design included an additional experimental group which, although restricted visually, were ambulatory, thus differing in the degree of deprivation experience. There were fourteen Ss in the severely deprived group, four Ss in the ambulatory group, and twenty in the control group. Visual, somesthetic and spatial tests were administered. The visual tests were given at pre- and post-isolation periods. The somesthetic and spatial tests were administered the 48th and 72nd hour of deprivation (thus altering, to some degree, the isolation environment). The tests were administered to all Ss prior to actually entering the cubicle to initiate the experiment for a seventy-two hour period. However, of the control group, only thirteen were tested for visual perception with the remaining controls being tested for spatio-somesthetic perceptual processes.

The method of deprivation was similar to the original McGill study. It should be noted that for eating and toilet purposes, it was necessary to move from one location to another. But the visual deprivation policy requiring the Ss to wear goggles, either translucent or opaque, depending on the condition, was adhered to at all times. Two cubicle Ss replaced the opaque masks and translucent goggles one hour prior to the termination of the experiment in order to determine and test for the effects of darkness on hallucinatory activity. The remaining Ss wore translucent goggles throughout the entire experimental period, as did the ambulatory Ss. As for the spatio-somesthetic tests, sixteen Ss, eight from the maximally deprived group and eight from the controls, were tested prior to entry of the experimental group into the cubicle, and at forty-eight and seventy-two hours respectively during actual confinement. Immediately following the confinement, the Ss were told to report on their visual perceptions. The quantitative visual tests of perception were then administered again. The results may be summarized as follows:

(a) There was no apparent effect on critical flicker frequency.

(b) There was an increment of figural after-effects as measured by the Kohler & Wallach test which measures the degree of displacement of two test figures.

(c) Size constancy was decreased as shown by the fact that the experimental Ss consistently selected larger discs when told to choose a disc which was the same size as the test disc.

(d) Tests for visual acuity showed a trend towards a significant improvement on the part of the experimental Ss.

(e) There was no apparent difference in brightness constancy.

(f) There was no change in the phinomenon.

(g) The autokinetic effect was increased for the experimental group.

(h) Color adaptation increased in favor of the experimental group.

(i) Shape constancy indicated a trend towards decrement as tested by selecting the triangle most closely approximating a tilting triangle of specific shape.

(j) There was no change in reversal frequency of the Necker cube effect.

(k) The movement of after-images increased for the experimental group.

All of the confined Ss and three of the four ambulatory Ss reported gross visual disturbances which disappeared within one-half hour. These disturbances were classified as follows:

(a) Spontaneous movement - undulating, shimmering, drifting, contraction or expansion of lines and/or objects.

(b) Induced movement - a change of object position with head and/or eye movements.

(c) Surface distortions - plane surfaces manifested a concave-convex sequential alteration.

(d) Linear distortions - when a point between two parallel lines is fixated, the lines seem to curve away from the fixation point. If the fixation point was above the line, the ends seemed to curve upward whereas if the point was below the line, the ends of the lines seemed to point downward.

In addition, exaggerated contrast, color saturation and luminosity, and enhancement or diminished depth perception were reported. These effects were observed under both monocular and binocular visual conditions, but most markedly under the latter.

As for the factors affecting hallucinatory experiences, it was noted that under diffuse conditions, nearly all Ss experienced vivid hallucinations . Of the two Ss who wore opaque goggles, only one experienced an hallucination during confinement. Upon exchanging the opaque with translucent goggles during the last hour of confinement, both Ss experienced hallucinations, the previously hallucinating S experiencing them even more vividly.

Another method of testing for perceptual disturbances was to place the Ss who experienced the most hallucinations with the translucent goggles in complete darkness. They reported a sudden brief increase in the vividness of hallucinatory experiences, followed by a decrease.

Upon reentry into a normal light environment with translucent goggles, there was an immediate resumption of perceptual disturbances to the original level of intensity. Two of the four ambulatory Ss with translucent goggles experienced vivid hallucinations. One of these occurred while the S was being walked to the restroom.

These results may be summarized as follows:

(a) Unpatterned visual stimulation seems to increase the probability of hallucinatory activity. However, unpatterned stimuli is not an absolute prerequisite.

(b) Since the perceptual disturbances were more severe in restricted Ss than in the ambulatory Ss it can be inferred that the functional disturbance is enhanced by restriction.

In order to determine the effects of isolation upon somesthesis, a tactual-form discrimination test and the standard two-point limen discrimination test were used. The results on the former demonstrated a significant decrement in the ability to discriminate geometric forms. The deterioration was related to the time spent in isolation. There was also a significant improvement in two-point limen discrimination.

On the spatial orientation tests, both paper and pencil and walking, it was observed that although the experimental group did not differ from the control Ss in distance estimation, they were inferior in terms of angle and direction orientation. In the "walking" test, the experimental group showed extreme confusion, many having difficulty in returning to the starting point. None of the disorientations were manifest in the control group.

These results demonstrate the great variety of perceptual disturbance generated by exposure to a hypodynamic environment. As for a tentative explanation of this phenomenon, Doane et al (1959) state that no complete satisfactory explanation is possible, but they suggest that hyper-excitability of the central nervous system should be considered. As a result of sensory deprivation, the "disused" systems become hypersensitized. Also, the random behavior of neural elements may conflict with the proper and stabilized organization of these elements to effect a normal perceptual process.

The two studies reported exemplify the type of research methodology in sensory deprivation conducted under Prof. Hebb's direction at McGill University. As previously stated, the basic essentials consist of a dimly lit, moderately large soundproof cubicle. The subjects wore translucent goggles to provide a uniform diffuse visual field, and arm-hand coverings to limit tactual stimulation. It was necessary for the Ss to sit up to eat, and to move to and from the bathroom, thus permitting some degree of mobility. The studies conducted by the Princeton group under the direction of Vernon et al (1958) were intended to be an extension, and not necessarily a replication, of the McGill studies. The difference lies in the modification of the physical aspects of isolation procedure, namely, that the cubicle was a floating, sound-deadened, completely darkened space whose size was smaller than that used in the McGill studies.

Six studies were performed to ascertain the variables accounting for the hypodynamic effects by manipulating variables in a particular order or combination to elicit maximal hypodynamic responses. The first employed four Ss under conditions of minimal deprivation for a period of 43 hours. Despite their being confined to an isolated cubicle, they had some social contact since their scheduled meals were brought in to them, and in order to use the rest room it was necessary that they be led there by one of the experimenters. Additional interruptions included the administration of learning tests. A 15 watt bulb was lit during testing, and also during the time the S ate his meal. The results indicated no perceptual or cognitive distortions based upon the verbal reports given by the Ss.

The second study, which employed eleven Ss, differed from the first in several ways. Food was stored in the cubicle which the S could eat ad libitum, but in darkness. However, toilet needs still necessitated the S's being led to a separate room. Of the eleven Ss, nine completed the experiment with five reporting at least two hallucinations and one subject reporting four. The reported hallucinatory experiences were categorized as follows:

Type I — Flashing, flickering, dim glowing lights which had no form appearing in the peripheral visual field.

Type II — Simple forms of definite shape, located in the central visual area.

Type III — Complex scenes depicting some movement, and resembling an actual visual experience.

No type III hallucinations were reported, whereas five type II and nine type I were experienced.

Since the decrease in sensory input from the first to the second study gave reason to believe that the severity of the confinement conditions was a critical factor in the production of the effects, further restrictions on sensory stimulation were made in the third study, which was to last for a period of ninety-six hours.

As in the second study, the cubicle was sound-deadened and completely darkened. Movement and social contact were further limited by moving the toilet facilities to a room adjacent to the cubicle. As stated previously, under no circumstances were the subjects permitted to make any sound whatsoever. The results indicated that of the nine Ss confined for four days, only one hallucinated. These subjects were confined in absolute darkness. In the previous study, the subjects were exposed to light leaks while being walked to the toilet. It was tentatively concluded that these brief exposures to light contributed to the higher incidence of hallucinatory activity reported in that study. In the fourth study, therefore, the influence of unpatterned visual stimulation was investigated. Ten Ss were isolated for a period of forty hours under diffuse, homogenous, unpatterned visual conditions, this being achieved by means of halved ping-pong balls placed over the eyes. The light was attached to a mask-like device so that head movements would not result in differences in intensity, as would result with a fixed light in the ceiling of the cubicle. However, this did not remove the intensity changes resulting from closing and opening the eyes. The food was prepared in bottles, and the S could eat ad libitum. The Ss were informed about the probability of perceptual distortions and the method of ranking them. Two Ss experienced type III hallucinations, but for only a few seconds.

Since this study did not yield the expected results, a fifth experiment was conducted to examine another stimulus variable, sound. A diffuse light was provided. A sound of constant intensity was presented by means of a hearing aid. None of the eleven Ss who remained in the experimental situation for the required period of forty-eight hours hallucinated. However, some reported that the bluish green color of the walls sometimes appeared to be a dark gray, but the blue-green shade was immediately restored following each eyeblink.

Finally, a sixth study was conducted to evaluate further the influence of light leaks since it was found that the most frequent hallucinations were reported during the second study, i.e., with the faulty blindfolds which permitted the light leaks. It was thought previously that the non-patterning of the stimulus was all-important, but the variable examined here was the effect of the discontinuous nature of the stimulus. Thus a panel was strategically placed in the room so that brief flashes of light could be observed by the S who wore a translucent mask. The headboard of the bed was lit up for two one-second periods during the eight-hour period. No S reported any hallucinatory effects.

Vernon's studies seem to indicate that there is no one single combination of stimulus conditions which invariably produces hallucinations. The low incidence of hallucinations and other effects, as compared to the findings of the McGill group, is puzzling. In an additional study, Vernon and McGill (1960) provided the S with a small view-box on one wall. When a button was depressed, a dim light lit two figures, a square and a triangle. A comparison between those who panicked following thirty-six hours of isolation against those who remained for the entire duration of the project (72 hours), revealed that the panic group pressed the button significantly more often than did the other group. This may indicate a greater need for stimulation in the panic group as compared with the non-panic group.

b. Reduced Stimulus Intensity and Patterning

Lilly (1956) developed a technique to reduce maximally the absolute intensity of physical stimuli. The S was suspended in a tank of slowly flowing water heated to body temperature. The S's head, held above water, was enclosed by a hood. The water temperature (95°-97° F) gave no differential sensation of warmth or cold; tactually, the subject was aware only of the mask and underwater buoyancy supports. The only sounds were respiratory and water movement.

The most profound feature of employing this technique concerns the rapidity with which the deteriorations occurred. The McGill type studies often required from many hours to several days to obtain the hypothesized maximal effects of deterioration. Lilly's report on the development of the effects may be summarized as follows:

1. For the first forty-five minutes, one is still aware of his surroundings and recent events.

2. One then becomes relaxed and shows more interest in the project at hand and the feeling that having nothing to do in addition to being alone seems to be very restful.

3. By the next hour, however, changes begin to occur. A "stimulus-hunger" develops in which subtle means of self-stimulation are pursued. These tend to abate the underlying tensions consideraoly as twitching muscles and slight physical movements against the water give some tactual sensation. Attempts are made to seek out methods of deriving satisfaction for the episode and it was found that prolonged inhibition of the movements tends to generate very pleasureful responses when later movements are made.

4. If this inhibitory period is resorted to for an extraordinarily long period of time, the subject in some instances may refuse to leave the tank, in which case it is necessary to force his removal.

5. Attention can become concentrated on the immediate stimulus objects, e.g., the mask, the suspension, or various parts of the body. One small aspect of these stimuli may become the total content of the consciousness of the individual, and may become unbearable.

6. If one has tolerated the situation up to this point, the next stage is a transition from concern with external stimuli and problems to reveries and fantasies which are highly personal. These may task the emotional stability of the S and may vary from complete suppression to euphoria.

7. In the subsequent stage the S begins to experience visual imagery. The mask, for example, may serve as a curtain for an extended stage beyond which one may "see" a dark, empty void before him. More intense concentration reveals small strangely shaped objects with "self-luminous" borders. Following immersion there was a time disorientation, the subject feeling as if he had just awakened. Another after-effect, primarily somesthetic, was the feeling of uncomfortable pressure on the body by the bed on the night of the day that the S was exposed to immersion.

These after-effects in some instances endured for several hours. A study employing Lilly's technique of water immersion was performed by Shurley (1960). Emphasis was placed on selecting Ss from a wide range of disciplines, from accountants to psychoanalysts. Both "normal" and "abnormal" subjects were included. Personal information was collected on each S and later selection was made on basis of ability to convey precisely accurate and detailed descriptive information to the experimenter. The experimental environment was carefully controlled, thus achieving a very minimal amount of light, sound, vibration, odor and taste sensations. The flowing water was held within a very narrow range of temperature variation with the S supported by a neck ring of extremely light plastic material for purposes of buoyancy. Inspired air was kept at a constant temperature as was humidity. Considerable effort was allotted to determine means of alleviating nearly all forms of pain and/or discomfort.

The Ss were thoroughly familiarized with each step in the scheduled series of events which constituted the framework of the project. However, the purpose of the project was never divulged. The Ss were assured that all information would be completely confidential. The subjects were told to be as completely uninhibited as possible in reporting their experiences. The Ss were also assured that they could terminate the project at any time.

The results indicate that free and spontaneous reporting under continuous immersion was markedly improved in that the detail was more concise, richer, and more uninhibited in terms of thoughts, imagery, and related deviations from the "norm". By comparison, the retrospective account, in most instances, differed considerably in that defense mechanisms seemed to be employed in terms of multiple repression since the post-immersion reports were not similar in quality and quantity to the reports given while under immersion. Ss having had analytic experience as compared to professional individuals who also participated in the same project were less repressive and illusive in their retrospective reports. The analysts gave more details which were similar to the reports given during immersion. In analytic terminology, the ability of the Ss to differentiate and describe accounts of a more primitive nature, i.e., primary processes, is usually more often repressed by individuals with well-developed defense mechanisms.

Difficulties were encountered in the evaluation of the reports. For example, one S reported that he was "using his left leg as a spoon to stir a cup of tea." He was also aware that his left leg was turning. Whether this is an antecedent to or consequence of the image is not clear. Another S stated she "saw" in the darkness, "a field of golden toadstools with the sunlight brightly reflecting from one of the stems." The latter seems to be a visual hallucinatory experience in what is a normal tri-dimensional "picture," whereas the former is indefinite in terms of real and image-like experiences of movement.

2. Other Studies

Cohen et al (1959) compared the effects of diffuse visual stimulation and absolute darkness in a study employing both normal and psychotic Ss, four of each for a total of eight under the same basic conditions as those in the McGill studies. It was expected that the diffuse group would experience greater effects than the opaque group. In the attempt to facilitate the onset of hallucinatory behavior, suggestion was given as a supplementary variable. The Ss were confined for only a few hours. The four normal Ss exhibited increased sensitivity to the stimuli within the room and a few simple hallucinatory scenes, whereas the psychotics manifested the typical vivid clinical hallucinations. The translucent goggles seemed to facilitate the onset of hallucinatory activity. However, the amount of visual sensitivity had no hearing or tendency to generate deteriorative effects on other sense modalities. In terms of cognitive processes, productive thinking, as measured by the word association test responses, did not falter under the stresses of the experimental situation. With respect to emotional factors, the normal subjects as well as the sole neurotic experienced heightened anxiety effects whereas the psychotics had least negative and most positive effects. The latter corroborates the findings of Harris (1959) that schizophrenics found the isolation experience a comfortable one.

Freedman & Greenblatt (1959) attempted to answer two general questions:

1. What is the relationship between perceptual distortions and hallucinations and other cognitive effects in a sensory deprivation study?

2. What is the result of varying the nature of the visual input and what does it do to these effects?

A number of college students volunteered to participate in the project and were thoroughly screened by the personnel office, the screening process consisting of psychiatric interview and autobiography. In order to minimize design contamination, the students were undergraduate students at the same university, upper third of their class, and non-psychology students. An additional precaution was to discard those who had previously participated in any kind of psychological experiment. Of a large number of candidates, twenty-seven males and three females were selected. The Ss were divided into three groups:

1. A non-patterned or diffuse light group.

2. A completely deprived group provided with opaque glasses.

3. A control group which was isolated, but with no sensory restrictions.

Groups 1 and 2 also had non-patterned auditory stimuli, and the project lasted for eight hours. Psychiatric and psychological tests were administered before and after the session. GSR and EKG were recorded intermittently and a one-way screen permitted observations to be made. The Ss were instructed to report any feelings and sensations, images and dreams. Following entry into the isolation chamber, communication ceased between Ss and experimenter. All verbalizations and/or sounds were recorded on tape. As in the McGill and Vernon studies, the Ss were placed in cubicles containing a cot with stored food, water, and toilet facilities readily available in an adjacent room. They all wore heavy cotton gloves and cardboard cuffs and earphones which carried white noise continuously, although the subjects reported they could hear doors slam, planes overhead, etc. The only difference between this group and one to be mentioned next was the fact that one group wore translucent goggles in a lighted room whereas the visually-deprived ("blackout") group wore opaque goggles under darkened conditions. The control group was merely isolated, with visual, auditory, tactual, and kinesthetic sensations being unimpared.

A pre-post test sequence was employed as follows:

a. Bender-Gestalt Motor

b. Visual perception (size, shape, optic illusions, and simple forms)

c. Depth perception (Howard-Dohlman apparatus)

d. Visual-Motor coordination (pursuit rotor)

e. Perceptual Lag

These tests were repeated as long as effects persisted following emergence from the cubicle The results on the tests are as follows:

a. Bender-Gestalt - All three groups demonstrated improvement; the control group performing significantly better than the "blackout" group.

b. Pursuit rotor - The diffuse and control groups demonstrated some improvement, the deprived group not performing as well.

c. Size constancy - No differences were significant. The diffuse demonstrated a trend in the way of larger lines and circles whereas the "blackout" and controls selected smaller objects.

d. Müller-Lyer - No significant differences.

e. Depth perception - No significant differences.

f. Reversible figures - The diffuse light group showed significantly more alternations on the face-vase figure. However, with reversible blocks this group showed fewer reversals.

g. Simple forms - Considerable distortions of all types were reported. For example, a triangle often appeared wavy and bent, and manifested a contracting-expanding effect with some segments appearing darker than others. The figures moved in various directions, but they had no set pattern of "movement" with the exception of arrow heads which "moved" from left to right. Persistence of the effects was up to five minutes. The diffuse group reported significantly more than the blackout or control groups.

The authors suggest the following mechanism to account for the distortions:

". . . the brain is more than a glorified computor passively accepting and analyzing external inputs . . . the fact that changes occur with both diffuse and blackout conditions indicates that it is the absence of order or meaning more than the specific nature of the stimulus field that tends to degrade perceptual organization. We must think in terms of an active process in the waking state that strives or seeks continuously and automatically to find ordered relationships in the perceptual environment . . . . We must postulate that it is this process of seeking order where there is no order and of attempting to incorporate n-1-order into previously existing schemata that accounts for the perceptual changes, instability and inconstancies . . . of the outside world. Our data suggest that these effects may be due to the release of tendencies inherent in the primitive perceptual process but normally held in check by a process of structuring and stabilizing the visual field."

Another approach to the analysis of hypodynamic conditions is that of Davis, McCourt & Solomon (1960), who asked whether the effects of sensory deprivation are the result of lack of stimulation per se or the lack of meaningfulness of the stimulation. Ten Ss were confined for ten hours in tank-type respirators according to the procedure of Mendelson & Foley (1956). The respirators were contained in a semi-darkened room and stimulation was further reduced by cardboard cuffs, constant auditory stimuli (tank motor) and the air-conditioned room. Light flashes from a 150 watt bulb were presented randomly. Perceptual effects were categorized as analogies, daydreams, fantasies, illusions and hallucinations, the latter being categorized following Vernon's (1961) system. A number of aberrations were reported, but a statistical comparison with the responses from two similar control groups yielded no significant difference.

Davis (1959) conducted an investigation in order to determine whether or not somatic activity is enhanced under hypodynamic conditions. He reasoned that minimal sensory input, if increased linearly, should result in a corresponding effect upon somatic activity. Therefore, the critical factor is the level of stimulation and not necessarily the variety of stimuli. Two groups of college students were selected, twenty-two in the control group and twenty-eight in the experimental group. The tank-respirator situation was used. The two groups were given a pre-isolation test for the variables measured, i.e., electrocardiogram (ECG), electromyogram (EMG), pulse volume, respiration rate, and skin conductance (GSR). A short term analysis of the data of both groups consisted of comparing recordings made five minutes prior to being exposed to deprivation conditions and recordings taken for one minute periods following five minutes and ten minutes exposure respectively to the deprivation conditions. The stimulus group had a 300 cps sound presented through earphones in addition to a very dim light for the minute of recording whereas the non-stimulus group had no stimulus presented. The results indicate a significant difference between the two groups in EMG activity in which the non-stimulus group demonstrated greater muscular activity than the stimulus group. There was also a slight difference in respiratory and circulatory activity, but the respiratory cycle is of particular interest since the non-stimulus group increased, thus indicating a possible apprehensive state with anxiety being induced by the severely restricted state of stimulation. In addition, the pulse volume exhibited a significant difference in that the non-stimulus group manifested a decrement and thus is indicative of an apprehensive state as inferred from vaso-constriction of the blood vessels. The data seem to indicate that the effect of stimuli reduces muscular and circulatory activity, but ~~increases~~ the respiratory rate whereas under conditions of constant sensory deprivation, the individual tends to a greater muscular and circulatory activity and inhibition of respiration, a pattern characteristic of apprehension. The results show that even a small amount of stimulation reduces the stress of a hypodynamic environment.

Mendelson & Foley (1956) studied the aberrant behavioral patterns exhibited by polio patients who were under treatment in tank-type respirators. It was noted that a number of patients developed cognito-perceptual distortions, hallucinations and delusions of many kinds. Extensive laboratory tests using normal subjects failed to yield data that would support the contention that metabolic or toxic products were responsible for the generation of the effects in the confined patients. These reports support previous findings that the effects were due to being confined in the respirator and exposed to decreased external environmental cues.

Since the meaning of the phenomena was in question, it seemed that more research was warranted in describing and defining more precisely these effects. The reports on eight patients is worth summarizing here.

1. A 22 year old female with involvement of the neck, trunk, and legs was well oriented until her fifth day in the respirator, when she became disoriented as to time, place and person. She had vivid auditory and visual hallucinations with the latter being tri-dimensional and in color. Her most vivid was that of being driven about the hospital in a car shaped like a tank-type respirator with her head protruding out of the trunk. In a few days, the symptoms ceased, but she continued having dreams which she could, however, distinguish rather readily from reality. Her dreams decreased in number and vividness after being removed from the respirator and transferred to a bed.

2. A 28 year old female with involvement of trunk, arms and legs was well oriented until her seventh day in the respirator, after which she began having hallucinations and delusions. They could be recalled with ease and clarity. Her most vivid hallucinations depicted her being carried about in a helicopter shaped like a respirator whose interior was entirely done over in foam rubber. Another scene placed her in a large ballroom where she is dancing alone, but there were many respirators scattered about which she had to dodge at all times during her dance. Another frequent and vivid scene showed her son and husband in respirators along either side of her own. The distortions were worse at night, and only when the ward was being cleaned or at meal times was she aware of her real environment.

3. A 31 year old male with involvment of the throat, trunk and legs had trouble recalling his attack, the initial hospitalization, and the events up to the fifth day of confinement. At this time, he began experiencing hallucinations and delusions which he was able to recall very easily some time later. He recalled that the experiences were more persistent and vivid as night approached with quiet and darkness pervading the ward. He interpreted these as dreams in which he was at home and the setting was tri-dimensional and in color. While at home, he cooked several things which he stated "tasted wonderful". He was aware of a neckplate or collar around his neck similar to that worn in the respirator and attempted on several occasions while in the hazy state to remove it. Another more vivid

"dream" involved his belief that the family car was stolen and he insisted that his wife call the police. This persistent thought endured for a number of weeks following his discharge from the hospital until he was certain the episode was not real.

4. A 34 year old male with involvement of legs and arms, with severe paralysis of his intercostal muscles, had poor recall of initial hospitalization and began having distortions about two days following placement in the respirator. He was poorly oriented at all times and dreamt he was traveling about the world in airplanes, on camelback, etc., and was able to verbalize his experiences and scenes in a travelogue manner. He did state that they were more numerous and vivid during the onset of evening when the ward was dimly lit.

5. A 31 year old male with total respiratory and quadriplegia paralysis was formerly engaged in tending vending machines. Immediately following placement in the respirator, he began experiencing "dreams" in which he was traveling about Boston tending to his machines, but a respirator was always in sight. In fact, many times the vending machine turned out to be an inverted respirator. During these experiences, the patient verbalized, employing terminology peculiar to his profession and often times used profanity when he encountered some difficulty servicing his "machines". The symptoms lasted fourteen days and were more vivid in the morning hours while being washed and/or attended by either his father or nurse. His recall of the experiences was very descriptive as he was able to recall small objects that were improperly positioned.

6. An 11 year old male with quadriplegia and later paralysis of respiratory muscles recalled being brought in the hospital and placed in the respirator, but became progressively more confused and disoriented. However, he did not report having any "dreams" until his seventh day after which he had them intermittently for the next ten days. They were rather vivid and repetitive, being more frequent at night. While visitors were nearby, he was fairly well oriented and conversed freely, but following their departure he would immediately lapse into a recurrent delusional state with both visual and auditory hallucinations. The dreams involved being driven home in his parents' car after which he would go to bed and fall into a deep sleep and wake up finding himself in the hospital. He was able to report in considerable detail the contents of his experiences. Upon being asked to reiterate his experiences weeks later when asymptotic, he did so with a very complete report of all the details he mentioned at the time while in the respirator.

7. A 43 year old female with involvment of the legs remained in the respirator for three weeks during which she had to be fed by nasogastric tube due to her unwillingness to take food orally. She reported being confused and following seven days in the respirator she began having a recurring "dream" during the night and early morning. She visualized riding down to the end of the street where

her mother and sister resided, whereupon she saw a gorilla towering above the housetops crushing the homes and persons in them. She saw her mother and sister running up the street where they were seized and killed by the beast, after which she attempted to get the respirator moving to evade the gorilla. She then found herself in the hospital and relating the story to the nurses in a very emotional manner. Her recall of the episode produced extreme anxiety. She reported it as being in color and tri-dimensional.

8. A 39 year old female with paralytic involvment of arms and legs had a very slow progressive paralysis of the respiratory muscles which required her being placed in a respirator seven days following her initial hospitalization. She was confused and disoriented and did not recall too well her being admitted. Three days following placement in the respirator, she began having vivid dreams depicting either her death or that of a relative. In the most vivid of these she recalled being operated on for a brain tumor and dying during the final phase of the operation. The oddity was that she had subjective feelings of the actual operation, yet was also an objective observer in the amphitheatre. She later recalled the events in the funeral parlor, the services, and final entombment in considerable detail. She recalled the events weeks later and it was the "sharpness" of the experience which made it difficult to differentiate from the real despite the lapse of many weeks.

A brief analysis of the patients' fantasies yield some interesting facts regarding the possible explanations for such episodes. Locomotion seems to be a strong wish-fulfillment component of nearly all the hallucinatory experiences, though this was sometimes denied. This suggests that the restriction on mobility is an important variable as to whether or not a S undergoing sensory deprivation experiences cognito-perceptual distortions. It would also appear as though the experiences were a sort of parade of events to occur in the future which depicts the patient and his tank respirator in a familiar environment. It is as if the patient were playing out a role regarding possible egodynamic alternatives to prepare him for a future stressful situation, thereby reducing the probability of exerting his tolerance levels to irreversible extremes.

These reports also reveal several other interesting events. First, only in those patients who were confined to a respirator did the "psychotic" symptoms appear, and they did not appear until at least two days had been spent in the respirator. The symptoms usually lasted for from ten to fifteen days following the initial onset of the distortive behavior. A specific trend was noted which began with a disorientation of time, place and person, which was intermittent throughout the total experience, which for the most part was interpreted as being real by all the patients. The most striking effect was that of machine locomotion where the patients thought they were being transported about in a car, train or helicopter shaped like a tank respirator.

Immobility appears to be an important factor in the generation of hypodynamic effects. However, to what degree or how it interacts with the other sensory conditions has not been clearly analyzed. It seems desirable to study this variable more thoroughly since movement within a space capsule will be limited.

A comparison of some of the conditions affecting the occurrence of hallucinations is listed in Table V-2 (from Freedman et al, 1961).

TABLE V-2

REPORTS OF HALLUCINATIONS UNDER
VARYING CONDITIONS OF MOTILITY AND VISION

	Experimenters	Motility	Visual Field	Hallucinations
a.	Wexler et al (1958)	Restricted	Monotonous, dim light	Yes
b.	Heron et al (1956)	Restricted	Homogeneous, diffuse	Yes
c.	Goldberger & Holt (1958)	Restricted	Homogeneous, diffuse	Yes
d.	Freedman & Greenblatt (1959)	(i) Restricted	Homogeneous, diffuse	Yes
		(ii) Restricted	Blackout	Yes
e.	Cohen & Silverman (1956)	Restricted	Blackout	Yes
f.	Vernon et al (1961)	Free	Blackout	(i) None (ii) Minimal
g.	Ruff & Levy (1959 b)	Free	Blackout	Minimal

A major task of this review was to attempt to identify the sensory modality which is most susceptible to hypodynamic conditions. Are the effects of visual deprivation more severe than auditory deprivation? Can activity or somesthetic deprivation alone produce deficits? The answers to these questions would permit appropriate steps to be taken in the effort to neutralize the hypodynamic effects. However, the literature is not clear on these points. The indications seem to be that visual deprivation, particularly the absence of interesting perceptual patterning, produces the most severe symptoms. The effects produced by a diffuse visual field are particularly striking.

It has also been found that light spots and patterns observed in dim light disappear and reappear unpredictably (Dunlap, 1921; Guilford, 1927; McKinney, 1963). This phenomenon has been related by McKinney to that of the disappearance of images which are stabilized in one position on the retina (Ditchburn & Ginsborg, 1952; Riggs, Ratliff, Cornsweet & Cornsweet, 1953; Pritchard, Heron & Hebb, 1960). These problems may appear if interior lighting is lost in the capsule. The possible effect of prolonged exposure to the high contrast visual conditions found in the space environment (cf. Rose, 1960) is also not known.

However, the auditory system has not been studied adequately, in that all the experiments have used masking noises. There are no data available on the effects of prolonged exposure to nearly absolute silence, such as may be obtained in a soundproof anechoic room. This variable may be particularly important since, if power is lost in a capsule in space, auditory stimuli could become reduced to very low levels.

Another area of research which seems relevant to the present space program is the determination of the minimal amount of information necessary to prevent hypodynamic effects. The conception of emergency devices to prevent hypodynamism would profit from a systematic study of this problem.

C. Neurophysiological Mechanisms

Any systematic attempt at the present time to infer the neural or chemical processes underlying the hypodynamic effects is premature. However, by taking certain recently available data from neurophysiology, experimental psychology, and psychological theory, some insight can be gained of the workings of the central nervous system and its interactions with the sensory systems. The value of such speculations is not merely theoretical or academic, but also that they may help lead to the generation of more meaningful experiments.

The evidence indicates that in general terms the environmental stimuli must be interesting to the subject in order to be psychologically stimulating. The organism soon adapts to the mere presence of or random variations in physical energy, and consequently the psychological stimulus value of such events is practically nil. In this respect it is useful to borrow some concepts from information theory: the psychological stimulus value of a given input is a function of its information content, not of the noise.

These behavioral observations can now be tentatively correlated with some recently discovered properties of the central nervous system. It is generally observed that when an organism is alert, the electrical activity recorded from its cortex shows a low-amplitude, high-frequency configuration, called the "activation" pattern (cf. Gibbs & Gibbs, 1950). When it is asleep or inattentive, the recorded brain waves are higher in amplitude and lower in frequency. When the mesencephalic portion of the brain stem is stimulated electrically in the sleeping subject, the activation pattern replaces the sleep waves, and the organism wakes up. On the other hand, when this portion of the brain stem is destroyed, in many cases the organism remains somnolent or lethargic, and its brain waves are of the high-amplitude, low-frequency variety (Lindsley, Schreiner, Knowles & Magoun, 1950). These and other data have led to the view that the brain stem, in the normal organism, exerts a facilitatory or dynamogenic effect on the central nervous system, particularly the cerebral cortex (Jasper, 1958). Furthermore, there are some data which show a correlation between measures of central nervous system activity level or 'arousal', and measures of performance (Malmo, 1954). These show that performance (cognitive and motor) is low both when arousal is very low (lethargic) and when it is very high (excited). The best performance scores correlate with the middle ranges of arousal. These relationships have led to the formulation of the concept of the 'optimum level of arousal' (Hebb, 1955). There is also evidence that collaterals of the sensory pathways converge in certain areas of the mesencephalic brainstem (Scheibel, Scheibel, Mollica & Moruzzi, 1955). These collaterals are the anatomical basis for the arousal effects of sensory information inputs. Adaptation to stimuli also seems to be a function of the brainstem (Sharpless & Jasper, 1956).

In addition to its arousal effects, another property of information may be termed its 'cueing' function, the significance being that neural events are thereby ordered sequentially. In a hypodynamic environment, these temporal cues are missing. It is probably significant, in this respect, that during sensory deprivation, subjects characteristically go to great lengths in the effort to keep track of time. Many means have been mentioned, such as counting the pulse into the thousands, and the attempt to order one's thoughts and images into a coherent sequence, can be interpreted to be a way of ordering time. In a normal environment, where objects move through space and sounds occur, information on time is available to the central nervous system. The orderly temporal sequence of external events support or pace, in some as yet unknown way, parallel or analogous events in the central nervous system (Hebb 1949, 1963). When the information input remains at a low level for many hours, the central nervous system, not having a steady input to process, seems to begin injecting information from its memory store, in the effort to provide the material by which its activities can be kept ordered. The central nervous system seems to operate on some time-dependent principle. Such autonomous activity is fairly coherent at first, but becomes more and more random. As the steps involved in the processing of information become progressively disordered or asynchronous, the temporally ordered processes required of normal cognition, perception, and movement begin to deteriorate. Many forms of aberrant behavior, such as feelings of depersonalization, hallucinations, and derangements, can be conceptualized as the occurrence of central neural events out of their normal temporal order. Conversely, effective cognition, normal perception, and accurate movement, are all functions of the appropriate ordering of neural events in time. Environmental events, as information, appear to provide a framework of temporal continuity by means of which thoughts and aims are oriented and ordered. An interesting area of research, both from the theoretical and the practical man-in-space points of view, is the determination of the minimal amount of information which is necessary to maintain normal neuronal timing.

D. Tests and Test Procedures

Although the literature on the effect of hypodynamic environments is confused and incomplete to an exasperating degree, there can be no doubt that the effects are real and of possibly great significance for the future space traveller. Such effects, while perhaps unimportant on short-term trips of a few months' duration, may become obtrusive during missions lasting several months or years. Also, as was mentioned earlier, another circumstance under which hypodynamic effects may arise is that following a component failure or mishap - loss of communications with earth, death or illness of the other crew members, loss of internal lighting and indicators. Without such inputs, the onset of behavioral deterioration may be rapid. It seems advisable to develop concepts and methods to prepare for such possibilities, the aim being to try to maintain the psychophysiological integrity of the remaining astronauts as long as possible, thus increasing the probabilities of survival and rescue.

In order to systematically study the hypodynamic phenomenon, with the purpose of meeting the needs of the projected man-in-space programs, it appears necessary to devise studies in which quantitative relationships between the stimulus conditions and the response parameters can be derived. By careful control and measurement of these factors, it may be possible to isolate the salient variable or variables. Steps to neutralize their effects can then be evaluated. In the following pages some of the considerations to be taken into account in the design of quantitative experiments in this area are reviewed.

As indicated by Thorpe (1961) and Wheaton (1959), present measures of response to a hypodynamic environment are primarily qualitative. Most of the quantitative measurements which have been made are physiological in nature, and are stress-oriented. These include studies by Burch & Greiner (1960) and by Davis (1959). The physiological parameters monitored have included electroencephalograph, electrocardiogram, galvanic skin response and catechol amine level of the urine. Studies by Goldberger & Holt (1958, 1961), and Holt & Goldberger (1959, 1960) are the major effort to date in analyzing the psychological aspects of the situation quantitatively. The results reported by the various researchers point up the necessity for a more quantitative and analytic approach now that the qualitative existence of hypodynamic phenomena has been demonstrated. The studies by Vernon (1961) which attempted to determine the optimal conditions for hallucination production were hampered by lack of adequate quantitative specification of the environment. Similar studies by Davis, McCourt & Solomon (1960) showed the same difficulty in specifying the conditions used and analyzing results. In general, the present status of the studies on hypodynamics, after more than ten years of work in the area, still shows a basic lack of the three elements necessary for good experimental results. These are listed by Woodworth & Schlosberg (1954):

1. Ability to produce the effect to be studied on demand.

2. Repeatability of observations by the experimenter and others.

3. Systematic variation of experimental conditions to permit study of stimuli on response.

A program to permit analysis of the effects of hypodynamic environments must meet the above criteria. Such a program should result in experimental work in which the physical stimuli are fully specified and the behavioral results are accurately measured. If this is done, it will be possible to determine the changes in behavior which accompany changes in the environment. It should also be possible to evaluate the degree of individual differences in response to an environment, and possibly to obtain useful correlations between responses on tests of individual difference and performance in specific hypodynamic environments.

Achieving such results will require accurate quantification of the physical stimuli, the test materials and the subject's responses to both. This quantification is necessary in any attempt to study ordered relationships among variables. Stevens (1951) gives a basic summary of the types of relationships which are covered by mathematical procedures. This use of mathematical specification can provide the necessary tools for better understanding of the effects of hypodynamic environments. The nature of the physical stimuli permits relatively simple quantification. Light level can be specified in terms of intensity, luminance, or other units (foot candles or foot lamberts are common). Sound can be specified by decibels (sound pressure or power) and by frequency analysis. Temperature and relative humidity are also easily measured. Tactile stimuli may be quantified along dimensions such as roughness, contact area and contact pressure.

Three other stimulus variables of importance are less easily handled. These are static and dynamic patterning and the meaningfulness of a given stimulus condition. The first two are physical variables, and can be measured in some degree. Static pattern can be specified in terms of the area, perimeter, angularity, regularity, solidity and various other parameters, as well as variability in relation to standard geometric forms and randomness. Movement of the sensory field, or dynamic patterns of objects in the field may be described mathematically, in simple linear cases by a velocity vector, and in more complex motion by a suitable descriptive equation such as a Fourier series.

The measurement of the meaningfulness of a particular stimulus configuration is particularly difficult, as meaning is the result of the interaction between the physical stimulus conditions and individual psychological factors. Obviously, meaningfulness cannot readily be measured directly. At best we can differentiate between responses to patterned stimuli of known high generally accepted meaning, and other randomly constructed stimuli which have an empirically determined low level of associative responses. Such low association response patterns should be fairly valid for group data, but may be considerably less so for an individual. This type of differentiation may be applicable in the study of the effects of patterns in a hypodynamic environment.

Measurement of the response also requires careful consideration. Accurate measurements of the response are required to permit inference as to changes in the organism. The responses to be measured may be divided into four classes: physiological, psychophysical, cognitive, and emotional. Physiological measurements include such parameters as electrocardiogram, electroencephalograph, electromyogram, catechol amine and metabolic activity levels. These measures are relatively easily quantified and analyzed. Psychophysical behavior refers to the performance of various acts which involve direct interaction with the environment. These would include reaction time, tracking tasks, and various coordinated maneuvers. Cognitive functioning is the term used to indicate tasks primarily involving complex mental activity such as problem solving and abstract analyses. The emotional measurements involve attitude and personality factors. These are by far the most difficult measures to handle qualitatively and analytically.

The effects of hypodynamic environments do not appear instantly, but develop over a period of time. Longitudinal experimental studies are therefore desirable to permit the study of the development of the phenomena. This requires that testing be performed during the hypodynamic period without disturbing the process by significantly changing the environment. Present data do not provide any indication as to what tests will meet this criterion. A preliminary set of parallel studies may be performed to evaluate tests for the longitudinal studies. A testing series should include pre-exposure and post-exposure tests plus varying amounts of testing during exposure to the hypodynamic environment.

In addition to the basic response description, the tests may provide a second benefit. This is the possible development of differentiation criteria to predict how individuals will react to a hypodynamic environment. The variability of individual responses to a hypodynamic environment is quite large. Some authors (Goldberger & Holt, 1958, 1961; Robertson, 1961 a b) consider this variability to be based on personality factors. Whatever the case, the variability may be predictable, and some of these tests may be of predictive value. In this area also, objective quantitative analysis is a must.

A third benefit of quantifiable tests is that the degree to which training can modify response to the hypodynamic environment may be determined. If we can accurately measure changes in response, then techniques for increasing tolerance to hypodynamic conditions can be tried and evaluated.

Individual differences are a major problem in the measurement of the responses to hypodynamic conditions. As is evident from the literature review, great variability in response is noted among subjects in all phases of the studies. Attempts have been made to analyze some of these variables. For example, Goldberger & Holt (1958, 1961) studied the scores on several projective and non-projective personality tests with what they termed "adaptive" and "nonadaptive" behavior. This behavior classification is psychoanalytic in orientation, making use of the concepts of the so-called "primary" and "secondary" thought processes. The major difficulty is in drawing quantitative relationships between these and environmental variables. A more experimental attack on the problem seems to be required in order to determine the interaction between the environment and the individual.

Some thought has been given to the requirements for tests which may be applicable to the present problem area. These are:

1. Quantifiability

   The test items should be objectively scoreable on either a discrete (yes-no type answers) or a continuous (position) scale. Where ranking is used, the scale intervals should be consistent (cf. Stevens, 1951).

2. Reliability

   The criterion of reliability is repeatability. A test which does not consistently repeat the scores or relative ordering of subjects taking the test is of relatively little use. Two common reliability test techniques are the split half (Spearman-Brown) and test-retest techniques (cf. Anastasi, 1954, pp. 94-119). The split half technique divides the test into two supposedly comparable halves and analyzes these. It is more a test of internal consistency than is the test-retest method in which the results of two successive administrations of the same or "equivalent" forms of the test are compared.

3. Validity

   The problem of test validity - does the test really measure what it is intended to measure? - is one of the most difficult and least satisfactorily answered in testing individual differences in response. The problem centers about the necessity of selecting criteria of behavior external to the test. This correlation between test score and behavioral criteria is the basis of most validation procedures. Anastasi (1954, chap. 6) describes some of the different types of validity measure used.

4. Standardization

   Most tests are standardized for "general population" norms with the intent of making them as useful as possible for the largest possible group of people, or for specific groups, such as those clinically described as mentally ill. While general population norm tests may apply in varying degrees to the highly selected astronaut population, the special group test standardizations are probably not very useful in their existing forms and with their present scoring.

In addition to the psychological tests, physological parameters have been monitored by some experimenters (e.g., Zubek & Welch, 1963; Zubek, Welch & Saunders, 1963; Cohen & Silverman, 1961; Mendelson et al, 1960). These have, in general, shown interesting correlations, such as a decrease in the recorded frequency of the electroencephalogram after extended exposure to hypodynamic conditions. However, the history of these techniques is plagued by difficulties in interpretation, great variability in type and degree of responsiveness among individuals, and methods of quantification and evaluation (Lacey, 1956; Martin, 1961). In his review Martin remarks:

"One cannot conclude on the basis of the researches reviewed in this paper, despite many suggestive leads, that any clearcut pattern of physiological-behavioral responses associated with anxiety arousal, distinguishable from other arousal patterns, has been demonstrated."

This is the classic problem of attempting to relate a particular pattern of physiological changes with a particular behavioral response. The difficulties seem to be mainly methodological, however, and the use of physiological monitoring in the study of hypodynamic effects is not discouraged. However, the difficulties mentioned cannot be minimized.

E. Summary

In this section a systematic and critical review of the literature on the phenomenon loosely-termed "sensory deprivation" was attempted. Since more than the manipulation of sensory stimuli is usually involved in such experiments, the more general term, "hypodynamic environment", is used herein. The objectives of the survey were (1) to analyze the evidence for the cognitive, perceptual and effective aberrations resulting from exposure to hypodynamic conditions, (2) to identify the environmental events associated with such effects, (3) to identify the sensory modality most susceptible to hypodynamism, (4) to evaluate the characteristics of individuals who are particularly resistant or susceptible to hypodynamic effects, (5) to evaluate the test methods of identifying and evaluating such characteristics, (6) to analyze the hypodynamic aspects or possibilities of the space capsule and the space environment, (7) to review some of the ways in which hypodynamic effects can be eliminated so that the reliability of man serving as a functional component in a space system can be improved, and (8) to point out areas where research, particularly the establishment of quantitative relationships between environmental conditions (input) and behavioral response (output), is needed.

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VI. CARDIOVASCULAR MODELS

A. Introduction

In this section, we present material on the problems of constructing models of the human cardiovascular system. The objectives in undertaking this work may be summarized as follows:

1. Construction of models of the human cardiovascular system which would be useful in predicting some of the effects of placing a human in a weightless state for prolonged periods of time.

2. Attempts to predict from the models design requirements for manned space systems.

3. Determining the minimal set of observable variables which will best describe the state of the vascular system as a function of time.

4. Determining means by which, at least theoretically, the performance characteristics of the cardiovascular system can be stabilized during the weightless state.

The mammalian cardiovascular system consists of:

a. A liquid tissue, the blood, which serves as the transport medium for certain nutrients required by the structures of the organism and for the removal of metabolic products produced by those structures.

b. A central pump for imparting to the blood the energy required to secure its passage through the circulatory system.

c. The circulatory system itself which is comprised of sets of conduits which conduct the blood to the various tissues of the organism.

These three items constitute the major elements of the essentially mechanical aspects of the system.

In addition to these mechanical aspects there are, as subsequent discussion will show, classes of sensitive control devices which serve to regulate the overall operation of the system under a very wide range of circumstances. Although at this juncture we do not wish to identify in detail the precise nature of what constitutes the controlled objects or features of the system, we note that one of the remarkable features of the mammalian organism noted many years ago by Claude Bernard is the constancy of the <u>milieu interieur</u>, that is, the essentially constant physical and

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chemical properties of the blood despite wide fluctuations in the external environment. This constancy is a partial result of the stabilizing mechanisms which regulate the performance of the cardiovascular system.

Because of the extreme complexity of its control mechanisms and the experimental inaccessibility of many of its parameters, the cardiovascular system has proven to be singularly resistant to experimental investigation even in the physiology laboratory. To gain experimental access to the system, the investigator is often forced to disconnect significant elements from their attendant regulatory mechanisms and then attempt to extrapolate his results to the intact organism. As in other fields of experimental biology, the skill of the investigator in defining the subsystem of interest so that its separation from the main system produces as little disturbance as possible, has been a major factor in the progress made to date.

B. Models of the Physical Phenomena

The complex problems of technique and interpretation posed by the experimental investigation of the cardiovascular system early led investigators to examine the feasibility of constructing models or analogs of the system.

Models of the cardiovascular system have taken many forms, but for the purposes of this report, we classify them as follows:

1. Physical models
2. Mathematical models
3. Electrical analogs

Of these, the physical models have almost invariably been hydraulic, or more generally, hydrodynamic systems incorporating pumps, reservoirs, and tubes for the conveyance of incompressible fluids through the system.

The mathematical models possess an ancient and honorable tradition in the physical sciences and in the last decade have begun to make significant inroads into cardiovascular physiology. The variety of mathematical forms taken by these models is enormous; examples of almost every structure of modern analysis are to be found in the literature of theoretical cardiovascular physiology.

The electrical analogs stand somewhere between the physical and mathematical models. On the one hand, the design of an electric analog is usually based on ideal mathematical relationships which must be formulated in detail prior to the construction of the system, while on the other hand, the analog once built will, like the physical model, manufacture departures from identity which may in a qualitative sense introduce complications into the interpretation of the output of the analog.

Physical models possess the disagreeable property that they are usually costly to build, somewhat cumbrous and slow to operate; most important, it is often difficult to modify the parameters of the model so as to examine its response over a range of conditions.

Despite these difficulties or drawbacks, physical models are often indispensable in the study of complex systems. For example, the mathematical analysis of complex valve systems and the interaction of valve design and turbulent fluid flow is a problem which still defies the best attempts of the fluid dynamicist. The only really satisfactory tool for the study of this class of problems is the construction and study of physical models and prototypes. Again, the naval architect, despite an enormous theoretical background, must still depend to a significant degree, on data collected in test basins on model hulls.

Mathematical models and analyses, of course, constitute a powerful - perhaps the most powerful - weapon available for the understanding and formulation of physical problems. They are, however, only approximations to the real world and are usually approximations over a relatively narrow range of the relevant parameters.

The formulation of a mathematical model is the special art of the analyst. Successful formulation, however, still leaves the analyst faced with the problem of obtaining solutions to the model. The history of the natural sciences is replete with examples of models which have successfully resisted the best effects of highly skilled mathematicians.

The advent of the modern stored-program digital computer, as well as the availability of electrical analog devices, has added a new dimension to the capability of the analyst in obtaining solutions to complex mathematical models. In fact, experience to date strongly suggests that sheer size alone, within certain limits, need no longer constitute a problem to the investigator insofar as the achievement of solutions to a properly formulated problem.

Despite the increase in problem-solving technology made possible by the advent of computing devices, the investigator is still confronted with the problem of verifying the range of validity of his model. Here the controlling word is range, because any arbitrary model will be valid at least at some arbitrary point in the dynamic response range of the phenomenon being studied.

Verification of a given model may frequently require knowledge of the values of experimented parameters which are of difficult accessibility. For example, in subsequent paragraphs, the central importance of cardiac outflow in the interpretation of certain data in cardiovascular dynamics will be discussed. Methods for measuring cardiac outflow in the intact organism are not available and, hence, the verification of models of the cardiovascular system in the intact unrestricted organism cannot be verified with respect to this parameter.

C. Plan of the Present Study

The organization of the present study is as follows:

1. An overall appraisal of the literature on mathematical cardiovascular physiology.

2. The specification of a mathematical model or set of models of the cardiovascular system with special emphasis on problems of manned space flight.

3. Certain broad scale simulations of the proposed model(s).

4. The construction, where required, of several physical analogs of certain components of the cardiovascular system.

5. The design of laboratory experiments in lower species (dogs) to verify certain of the system characteristics.

D. Major Features of Cardiovascular System

Although the major events of the cardiac cycle are well known, it is desirable to briefly review them here because our concern will be to consider the system as a feedback device. Consequently, we shall want to identify the regulated or controlled quantities.

In Fig. VI-1 we present a schematic diagram of the cardiovascular system. Venous blood, e.g., blood which has delivered up a portion of its oxygen to the tissues and has been loaded with carbon dioxide, is collected at the vena cava under low pressure (2-3 mm Hg). Under this pressure head, the relaxed right atrium fills and, upon contraction, forces the volume of blood into the right ventricle. The right ventricle then acts as a pump to force the venous blood through the lungs, where it is reoxygenated. From the lungs, the oxygenated blood is drained to the left atrium which in turn delivers it to the main pump of the circulation, the left ventricle. The powerful left ventricle then ejects the blood into the main circulation through which it travels to various structures of the organism and eventually returns to the right ventricle. The heart, therefore, consists of four pumps. Thses pumps are automatically and electrically bound together, so that, under normal conditions, their action is well synchronized to prevent any pooling or stagnation of blood in either the right or left side.

The cardiac cycle is divided into two main events, namely, diastole and systole. During diastole, the whole heart is relaxed, and its various spaces fill with blood. Diastole ends with the simultaneous contraction of both atria, in which blood is forced into the ventricles. This is the so-called atrial systole. The systolic phase consists of the actual ejection of the blood out of the ventricles and into the pulmonary, or systemic circulations. In Table VI-1 the major events of the cardiac cycle are presented.

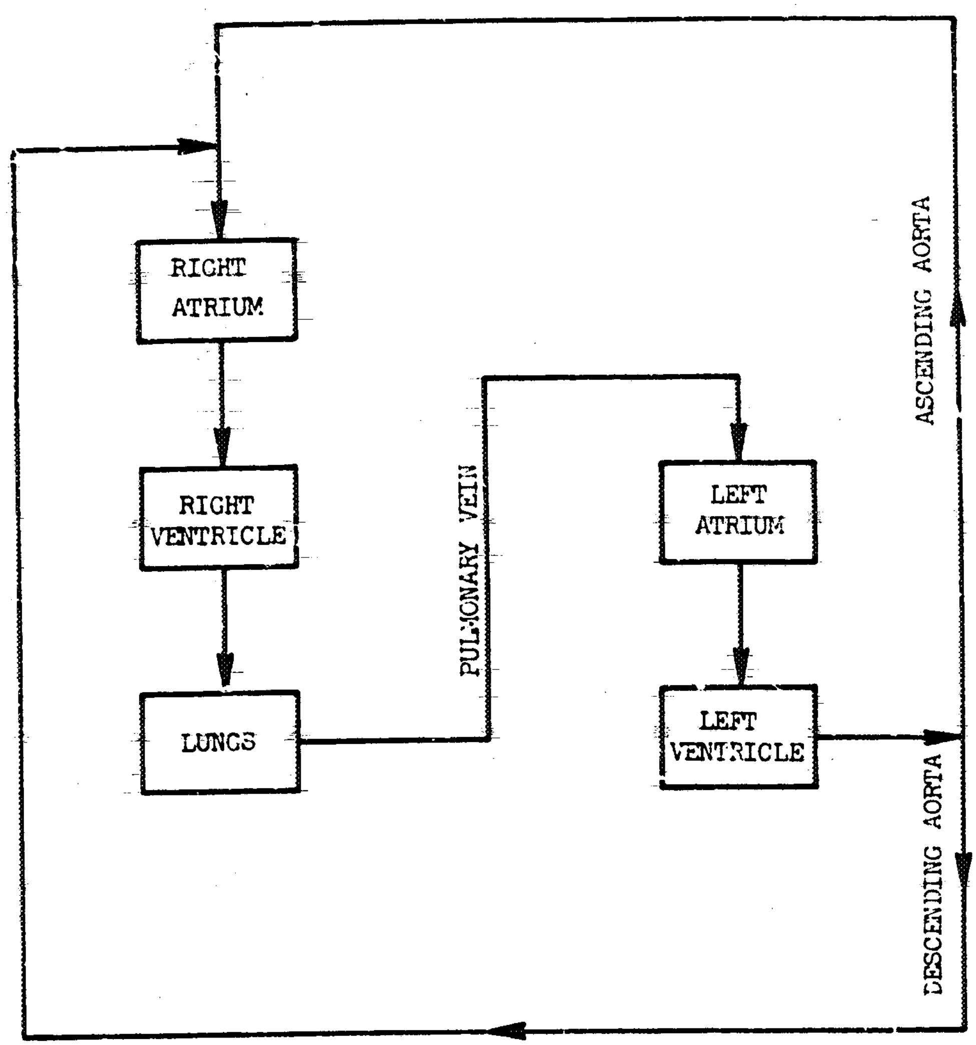


Fig. VI-1 Schematic Diagram of Cardiovascular System

As suggested in Fig. VI-1, the arterial and venous sides of the main ystem circulation are separated by flow impedances, which physically are mprised of the small vessels and capillaries which penetrate the anatom- al structures and are the actual sites of oxygen/carbon dioxide exchange.

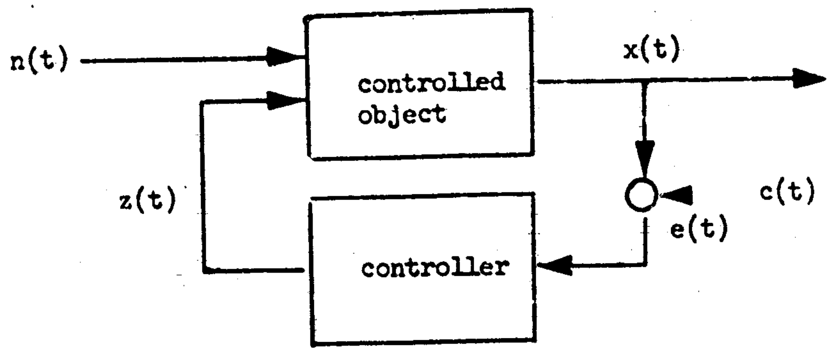
TABLE VI-1

COMPARISON OF DURATION OF EVENTS OF CARDIAC CYCLE IN MAN AND DOG IN MILLISECONDS

ent	Man	Dog
ometric Contraction	50	50
ximum Ejection	90	120
educed Ejection	130	100
Total Systole	270	270
rotodiastole	40	20
sometric Relaxation	80	50
apid Inflow	110	60
iastasis	190	290
trial Systole	110	110
Total Diastole	530	530

. The Cardiovascular System as a Feedback System

In the following sketch we show the major components of a feedback ystem. The system is divided into two major elements, e.g., the controlled bject and the controller. The output of the controlled object is a time arying quantity $x(t)$. The current value of $x(t)$ is sensed at the output nd compared to $c(t)$ the command or set level, to yield the error $e(t) =$ $(t) - c(t)$ which is processed by the controller whose output $z(t)$ is a unction of $e(t)$. This control signal $z(t)$ is fed back to the controlled bject to readjust its output $x(t)$.



In addition to changes in c(t) the system is subjected to "perturbations" n(t) which are more or less random in nature. Since these perturbations propagate themselves to a greater or lesser extent into the output x(t), it is necessary that the controller be so arranged that its response time and other characteristics be such that the controlled object's performance be quickly adjusted for changes in both n(t) and c(t).

In case the system is linear, that is the output of any component is related to the input by a system of ordinary linear differential equations, a theoretical analysis of its response characteristics can be arrived at by relatively simple techniques.

Actual physical systems are never linear, owing to departures of the components from ideality, hysteresis effects, etc. The important question, however, is not whether the system departs from ideality but rather the magnitude of these departures. Many instances are known in which the application of linear techniques to the system yield results which are satisfactory approximations to the actual performance.

In our analysis of the cardiovascular system we shall frequently assume linear behavior of the system components. Nonlinearties will enter the model through parametric control.

F. Review of Current Theoretical Cardiovascular Physiology

In Fig. VI-2 we show a simple hydraulic system in which fluid is forced by a pump through a resistive element from whence it flows back to the pump. In order to control fluid flow through the system we have at our disposal three variables which we can regulate, pump frequency F, stroke volume V_s, and resistance R.

In an analogous manner the functioning of the cardiovascular system appears to be regulated through control over these variables.

Grodins (1959) in an important and basic paper has attempted to integrate certain of the known facts about the cardiovascular system into a mathematical model. Because of the importance of this and later papers we shall briefly review the model.

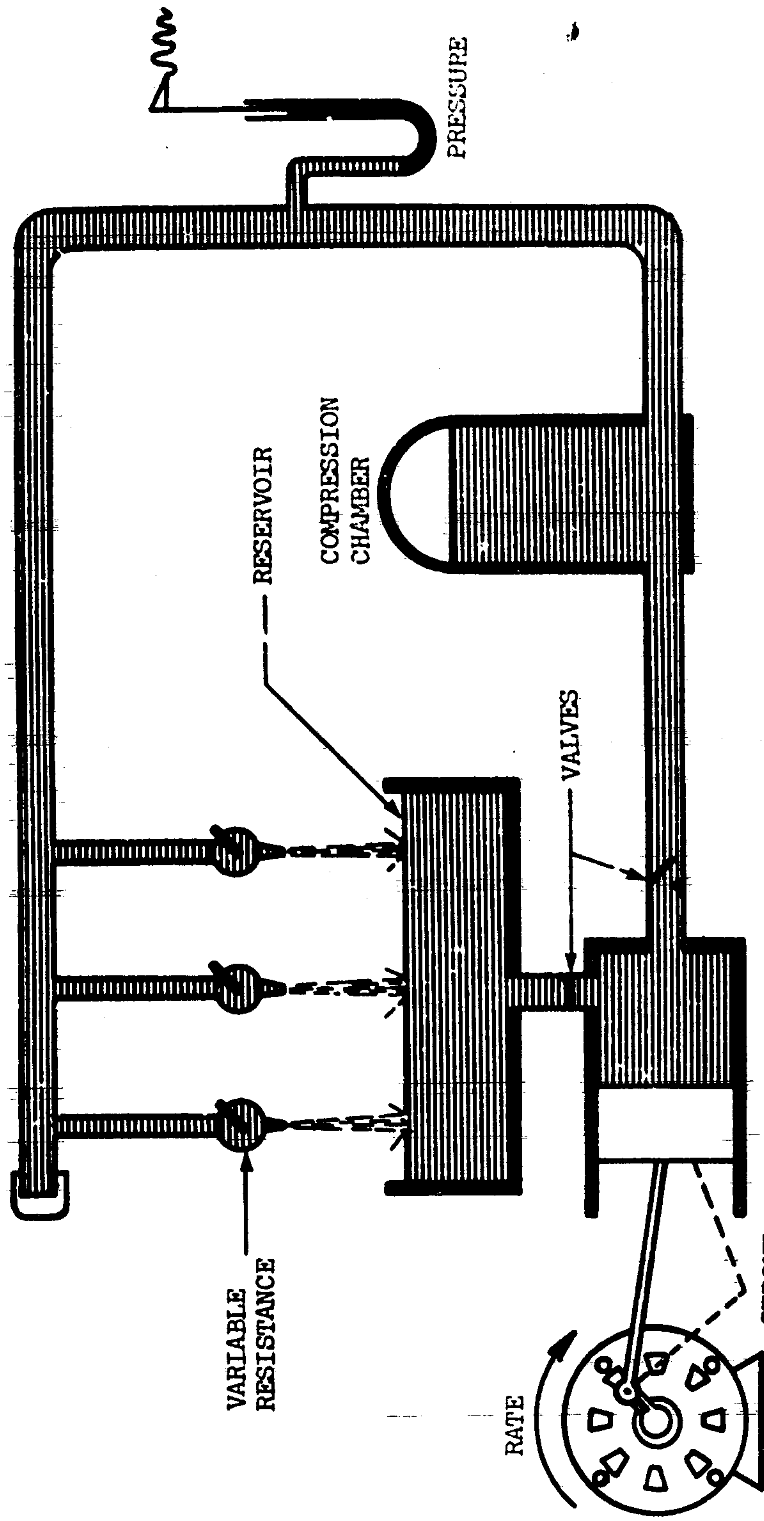


Fig. VI-2 Hydraulic Model of Circulatory System

Consider first an isolated ventricle. We assume that the useful work of the ventricle is proportional to diastolic volume V_S:

$$w = S v_s \tag{1}$$

where the constant S is the so-called Starling constant (Delund 1962). Since residual ventricular volume V_R is the difference between diastolic and stroke volumes, i.e.,

$$v_r = v_d - v_s \tag{2}$$

we have

$$w = S(v_d - v_r) \tag{3}$$

We may equate the work to the product of the mean arterial pressure load Pa and Vd - V_R to obtain

$$v_r = [1 - (S/P_A)] v_d \tag{4}$$

Equation (4) represents the emptying law of the isolated ventricle. Ventricular filling laws may be obtained from

$$RC\dot{v}_d + v_d = CP_v \tag{5}$$

where R denotes filling resistance, C the ventricular compliance (a constant) and P_V is the mean venous pressure. The solution of (5) is

$$v_d = CP_V + (v_r - CP_V)e^{-t/RC} \tag{6}$$

Writing

$$k = e^{-[(60/F) - 0.2]/RC} \tag{7}$$

$$A = 1 - k \tag{8}$$

where F denotes cardiac frequency in cycles/sec., permits substitution of equation (4) and t = 60/F - 0.2 into equation (6) which yields

$$v_d = CAP_V/(1 + k[(S/P_A) - 1]) \tag{9}$$

Finally, using (2), (3), and (4) we obtain

$$v_r = CAP_V(P - S)/[AP_A + Sk] \tag{10}$$

Ventricular output Q is

$$Q = FV_S \tag{11}$$

Consequently, using (6) and (10) we obtain

$$Q = FSCAP_V(AP_A + Sk) \tag{12}$$

Equation (12) constitutes Grodins' expression relating average cardiac outflow to the venous and arterial pressures.

Turning now to the circulation, Grodins assumes that the circulatory system can be described by

$$C_{AS}\dot{P}_{AS} = [Q_L - (P_{AS} - P_{VS})/R_S] \tag{13a}$$

$$C_{VS}\dot{P}_{VS} = [-Q_R + (P_{AS} - P_{VS})/R_S] \tag{13b}$$

$$C_{AP}\dot{P}_{AP} = [Q_R - (P_{AP} - P_{VP})/R_P] \tag{13c}$$

$$C_{VP}P_{VP} = [-Q_L + (P_{AP} - P_{VP})/R_P \tag{13d}$$

where the subscripts VS, AS, AP, VP denote the venous systemic, arterial systemic, arterial pulmonary, etc. lumped circulations and Q_L, Q_R refer to expressions identical to Equation (12) specialized for the right and left ventricles.

Using this model equipped with an arterial baroceptor loop Grodins and his associates 1961 have compared their output with those obtained from laboratory studies in dogs. They compared open command forcing in which the carotid sinus baroceptor areas were forced by an arbitrary function and open and closed loop load forcing in which the total blood volume in the circulation was changed arbitrarily. Since it is known (3) that the output of the baroceptors is mediated via the medullary cardiovascular centers to influence both the cardiac frequency F and the systemic resistance R_s suitable representations of the functional dependence of the values of these parameters on P_{AS} were included in the model.

In addition to the above "dynamic" control studies, Grodins also examined the implications of the model under static conditions under a variety of load conditions. These conditions were

1. Normal Operating Conditions
2. Blood Volume Changes
3. Changes in Resistances
4. Changes in Cardiac Frequence
5. Myocardial "Weakness"
6. Normal Exercise

In general the agreement between the output of the model and arterial experimental results was remarkably good. In particular, the response to step changes in blood volume and changes in peripheral resistance as well as a comparison of the response to changes in cardiac frequency were remarkable. Studies on the effect of weakening the mycardium were also undertaken, and here again the agreement between the model and observations made on a heart lung preparation were in excellent agreement.

Defares et al (1962) and Hara 1962 have mechanized versions of the model outlined above for computation on an analog computer. Both groups, however, introduced significant improvements in the degree of realism of their models by providing the system with gates to simulate the action of the heart valves. In addition, Hara provided his model with a left and right ventricle in which the ventricular compliance changed as a function of time thus conferring upon the structure an inherent contractability.

The models described above are, as their authors note, only broad approximations to the physical system. There are several obvious and important deficiencies which would need to be rectified before they would serve as useful tools for the prediction of phenomena in the weightless state.

Perhaps the most important item is the inclusion of a model of coronary blood flow in the overall system. In Equation (1) it is reasonable to assume that the starting constant S, as well as Vd are in some way related to the integrity of coronary flow. Models of the heart action generated by McLeod (1962) have attempted to derive models of ventricles which obey Starling's law but these authors did not include a coronary circulation.

A second and perhaps equally important defect in these models is the absence of a functioning lung and the chemoregulating capability that this provides to the system. In these models the lung is regarded as an essentially passive resistance. Again, while the literature contains a number of models of pulmonary gas exchange no cardiovascular model to our knowledge has yet incorporated such a model in the system. A third component lacking from these models is the absence of an aortic capacitance.

The ascending and descending aorta act as a third ventricle. Blood ejected by the left ventricle during systole causes potential energy to be stored in the walls of the aorta. This potential energy is then converted to kinetic energy of flow which tends to force the blood toward the periphery.

Karreman has shown that the aorta can be treated as a two-chambered elastic system connected by an inelastic passage. This approach has been developed by Roston with several interesting consequences.

Roston (1959, 1962) assumes that the output of the left ventricle can be represented by the positive arch of a sine function. Thus

$$Q_L = \sum_{n=0}^{\infty} \Big[b\,u(t-na)\sin(m\pi/a)(t-na) + b\,u(t-na-a/m)\sin(m\pi/a)(t-na-a/m) \tag{14}$$

where

$$u(t-na) = 0,\ t < na \qquad = 1,\ t \geq na \tag{15}$$

$$u(t-na-a/m) = 0,\ t < na+a/m \qquad = 1,\ t \geq na+a/m \tag{16}$$

Writing

$$\dot{P}_1/k + P_1/R = Q_L \tag{17}$$

for the pressures P_1 and P_2 in the ascending and descending aorta, respectively, Roston obtained explicit representation of P_1 and P_2 as functions of time. Because of their complexity, these functions are not included here. Several conclusions of interest were reached from a study of the solutions to Equation (17). First, P_2, the pressure in the descending aorta may exceed P_1 during most of the cardiac cycle, and P_1 and P_2 do not bear any fixed relationship to each other. In clinical practice, blood pressure is measured from the subclavian and brachial arteries. The mathematical representation of this pressure will be the same as P_2, and since the latter bears no particular relationship to P_1, clinical measurements may be expected not to give accurate estimates of pressure in the ascending aorta.

Roston also investigated changes in duration of cardiac cycle and duration of systole with fixed cardiac frequency. As the cycle lengthens, with cardiac output fixed, the peak systolic and the diastolic pressures decrease. On the other hand, lengthening of the systolic interval decreases the peak systolic pressures but increases end diastolic pressures.

This finding may be of importance in cardiovascular homeostasis. The lengths of the QT interval in the human electrocardiogram is approximately constant x a, where a is the duration of the cardiac cycle. The QT interval represents electrical ventricular systole which in turn reflects duration of systolic ejection from the ventricles. Thus, as the heart rate slows, the duration of systole increases and this increase, as noted above, increases end diastolic pressure. Since most of the flow of blood through the coronaries occurs during diastole and since coronary flow is driven by diastolic pressure, these changes tend to stabilize coronary flow. If, as seems reasonable to suppose, Starling's constant S is, in part, a function of the integrity of coronary flow, then failure of the heart rate homeostatic mechanism could be expected to initiate a series of reactions which would lead ultimately to ventricular weakness.

G. Cardiac Feedback Mechanisms

Three major feedback loops appear to be operative in the regulation of cardiovascular function. These are: (a) heart rate control mediated by pressure changes in the carotid sinus, (b) regulation mediated through oxygen and carbon dioxide partial pressures in the blood, and (c) changes in peripheral systems. Warner (1958) and his associates, and Clynes (1962) have investigated the pressure receptor feedback mechanism. Warner sensed arterial pressure in the carotid sinus of the dog and processed that signal according to $\dot{P} + KP = N$ to generate neural action potentials which were inserted into the cardiac branch of the vagus nerve. He found that because of the delay in the responses of arteriolar smooth muscle to carotid sinus stimulation, the amplification of carotid sinus activity aggravates rather than diminishes arterial pressure variations at certain forcing frequencies. He attributes this to the response time lags in the effector organs. Warner found that the differential $\dot{P}$ played no significant part in the response of his system.

Clynes has advanced a theory which suggests that biological systems are, in general, nonlinear due to the fact that the systems exhibit unidirectional rate sensitivity; that is, owing to the fact that almost all known biological responses in mammals are initiated through the release of chemical substances, and since the concentration of a physical substance must always be , it is not possible to have negative concentrations as one has negative voltages. Therefore, it is impossible to cancel a response once initiated. Furthermore, responses to positive or negative impulse functions are in the same direction.

One of the phenomena analyzed in terms of this theory is the phenomenon of respiratory sinus arrhythmia in which the heart rate is affected by the respiratory movements of the chest. As a result, Clines was able to interpret his results in terms of a feedback system and predict regular and irregular heart rate changes due to respiration for any manner of breathing in a given subject.

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It is not hard to see why the literature contains a paucity of models of cardiac regulatory feedback mechanisms. The extreme complexity of the mechanical system as exemplified by even the relatively simple model, makes it extremely difficult to quantatively deal with the synthesis and analysis of a satisfactory control device. Furthermore, many of the parameters required for insertion into a model are experimentally unavailable. Even in those cases where static measurements are possible on, let us say, peripheral resistances, it has not yet been possible to experimentally determine the functional dependency of this variable on some other quantity, such as pressure.

H. Effects of Weightlessness on Cardiovascular Dynamics

We turn now to the major point of this report, namely, what is the source of the observed discomfort reported to follow prolonged periods of prolonged weightlessness.

First, we note briefly the following facts: in a recumbent person in a 1 G environment the blood flow through the brain is about 750 ml. per minute while the corresponding oxygen consumption is approximately 45 ml. per minute. Thus the brain, representing about 2% of the body weight, ordinarily receives about 16% of the cardiac output and about 20% of the oxygen consumed by the body in a basal state.

Since the brain tissue stores little glucose or oxygen, even brief cessation of cerebral blood flow produces rapid loss of consciousness. It may, therefore, be reasonably supposed that maintenance of cerebral flow is vital to survival of the organism and must be maintained at a nearly constant level.

The brain is unique in that cerebral circulation takes place in a rigid case, the skull, and therefore the combined volume of brain, blood and cerebrospinal fluid must remain constant. The actual effect of G-forces on the cerebral blood flow may be likened to the introduction of a back e.m.f. into a circuit. Thus a normal person standing on a surface in a hypothetical weightless state would, if the cardiovascular feedback systems were inoperative, manifest a mean pressure in the carotid arteries of about 100 mm Hg. On the other hand, the same person suddenly inserted into a 1 G environment would experience a drop of about 40 mm Hg.

It seems likely that some degree of cardiac embarrassment is likely to ensue when a human is brought from a 0 G to 1 G environment. The reimposition of G forces on a venous system that has become accommodated to a lower gravitational load would lead to a decrease in venous return. Such a decrease in venous return would have to be compensated by (a) an increase in heart rate, (b) an increase in stroke volume, and (c) an increase in resistance. The preponderance of evidence points to an increased heart rate as the main adjustment. Now, if the resistance to flow is accommodated to a lower load then it is possible that the left ventricle cannot maintain a sufficiently high diastolic end pressure to avoid some degree of myocardial ischemia. This in turn might lead to a shift in the Starling constant and hence a transitory myocardial weakenss as suggested by Roston.

I. A Mathematical Simulation of the Cardiovascular System

In order to examine the possible effects of changes in gravitational loading on the functioning of the cardiovascular system, a model of the cardiovascular system Figure VI-3 was formulated in terms of an electric analogy, and certain of its salient features examined mathematically. This model does not depart greatly in spirit from those proposed by Grodins, Hara or Deland. It contains, however, a division of the systemic circulation into two major subsystems-the cerebral and non-cerebral systemic vessels.

Because of the absence of data on the time variation of the various parameters entering into this model, it was not considered worthwhile to subject this to a full-scale simulation at this time, pending the completion of animal verification of the circuit parameters now in progress. Instead, a simulation was performed on the cerebral loop to qualitatively determine the effect of sudden loading and unloading of the system by G forces. Since the system is nonlinear, owing to the presence of diodes, the detailed mathematical analysis is not presented here. The discussion will be in terms of the output of the simulation shown in Figure VI-4.

The circuit elements are as follows:

W_2 = Pressure of Heart
R_3 = Resistance of Heart
D_4 = Aortic Valves
C_2 = Aortic Capacitance
E = Gravitational EMF
R_6 = Cerebral Resistance
D_5 = Return Valve
R_5 = Systemic Resistance

Figure VI-5 shows (curve 1) the form of the pressure output of the left heart while under gravitation, and curve 2 shows the simulated aortic blood pressure under the same load.

Figure VI-6 (curve 1) shows cerebral blood flow under gravitation, and curve 2 shows the same quantity after sudden insertion into a 1 G environment. As expected, blood flow is diminished, or nonexistent. Since it is known that heart rate is increased under such conditions, it was of interest to examine the response of the system to such increases.

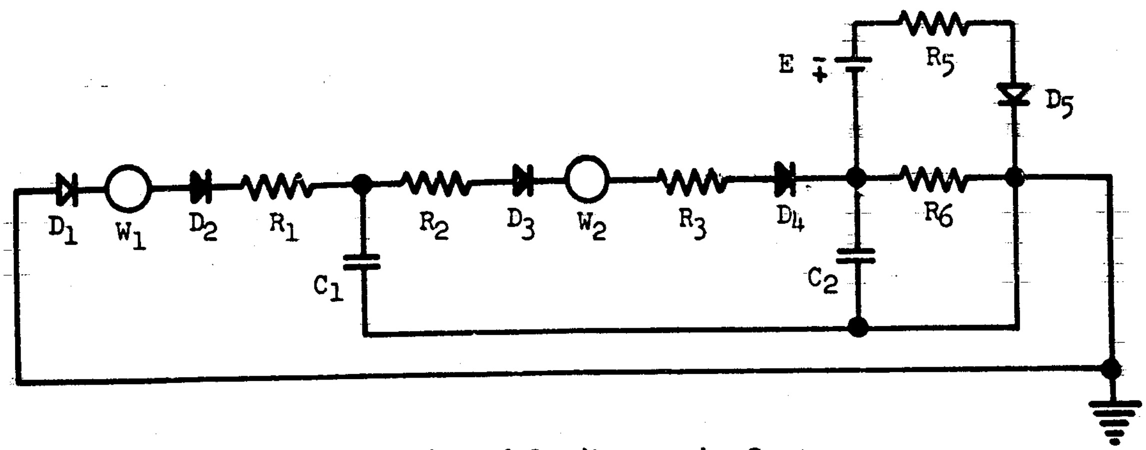


Fig. VI-3 Electric Analog of Cardiovascular System

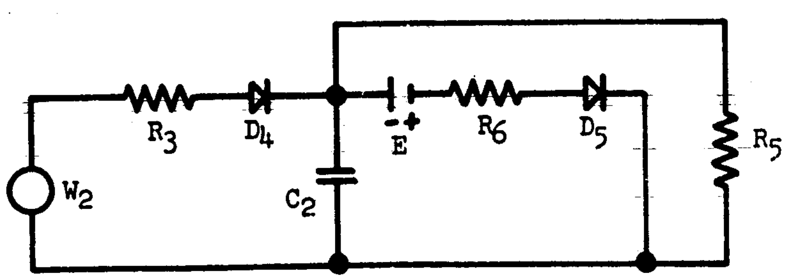


Fig. VI-4 Electric Analog of Cerebral Circulation

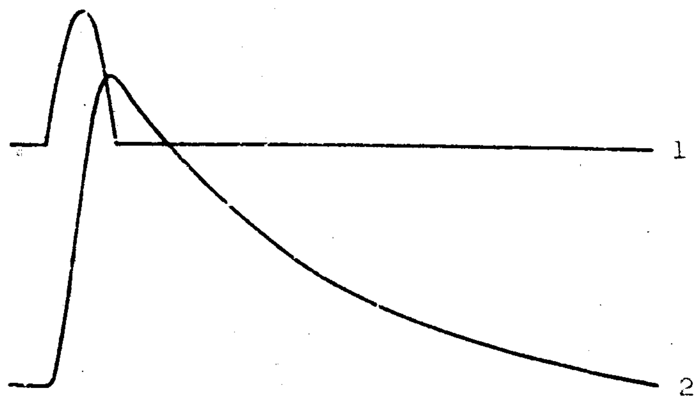


FIG. VI-5

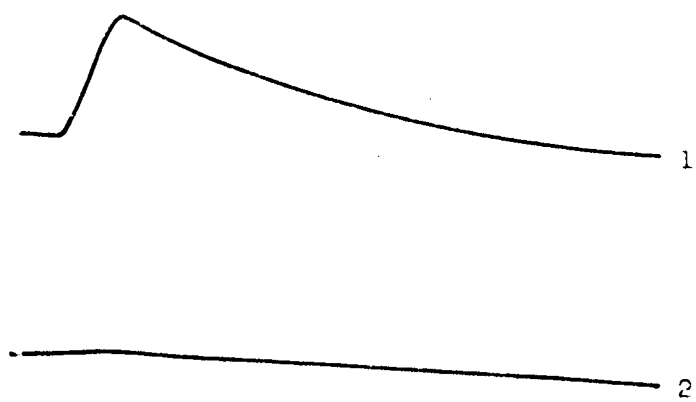


FIG. VI-6

Figure VI-7 shows (curve 1) blood flow through the cerebral circulation under 0 G conditions. Curve 2 shows the greatly diminished blood flow after sudden application of G forces. Curve 3 demonstrates the response of the system and the substantial correction of blood flow due to a doubling of heart rate. It is interesting to note that two-fold increase in heart rate is not sufficient to completely restore cerebral flow to its previous level before the application of the G forces.

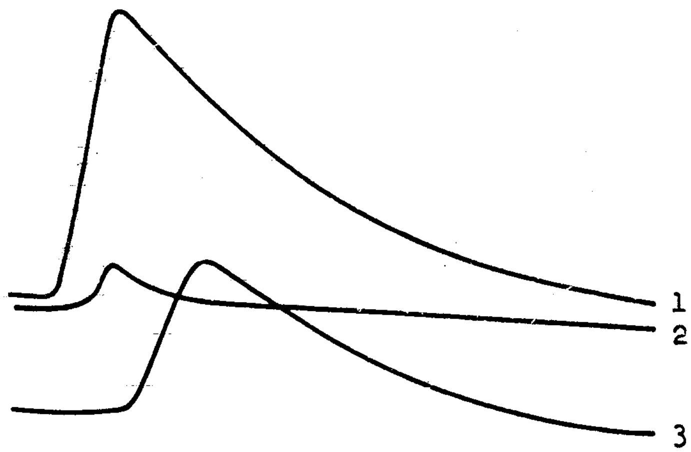


FIG. VI-7

In Figure VI-8 the simulated responses of the system to changes in ventricular pressure are shown in seven equal steps over a range zero to essentially maximum output. It will be noted that the cerebral blood flow is fairly sensitively dependent in a complex manner on cardiac output.

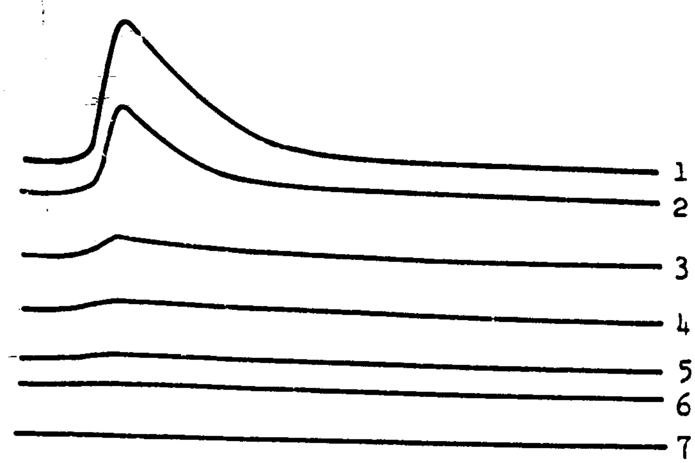


FIG. VI-8

In Figure VI-9 is shown the relationship between heart rate amplitude, pressure amplitude and systolic duration. Curve 4 shows the cerebral flow just after the sudden application of approximately 1 G. Curve 2 displays the corrective action of increasing the heart rate while holding amplitude and systolic duration constant. Curve 3 shows an effect of doubling the amplitude of the heart with the same heart rate as Curve 4. Curve 1 displays the changes due to increased systolic duration.

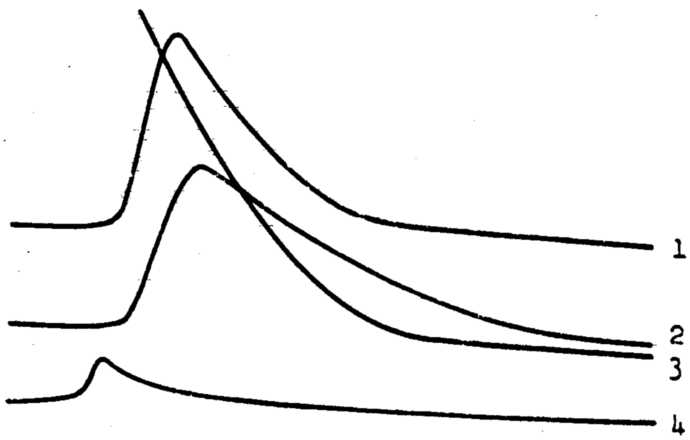


FIG. VI-9

J. Mechanical Analogs

Figures VI-10 and VI-11 show some overall views of a mechanical pump designed to study pressure relationships in a system of tubing. The purpose of the construction of this cardiovascular model is the study of liquid flow into and out of a valved pump. Since the flow of liquid tends to become turbulent in the ventricular chambers, it is difficult to study this type of problem mathematically or electrically.

As the results of further system simulations and animal experiments become available, this mechanical model will become increasingly useful as a convenient tool to explore pump dynamics under realistic conditions. Such pumps to be effective require an intrinsic servo control, that is, pump rate must be controlled to keep pace with venous return so as not to empty the system. Included as an addendum to this section of this report is a paper from the University of Pennsylvania Harrison Department of Surgery on work performed under subcontract to study and explore means by which such servo devices can be implemented. The theory that this device has proven most useful in providing insight about one of the means by which the right and left heart is synchronized in actual performance.

K. Discussion

In this report, we have not attempted to summarize the monumental literature which has accumulated in the past 100 years on the pulsatile and non-pulsatile flow of liquid in elastic tubing. Rather, we have concentrated on integrated models of the cardiovascular system. Our reason for this selection

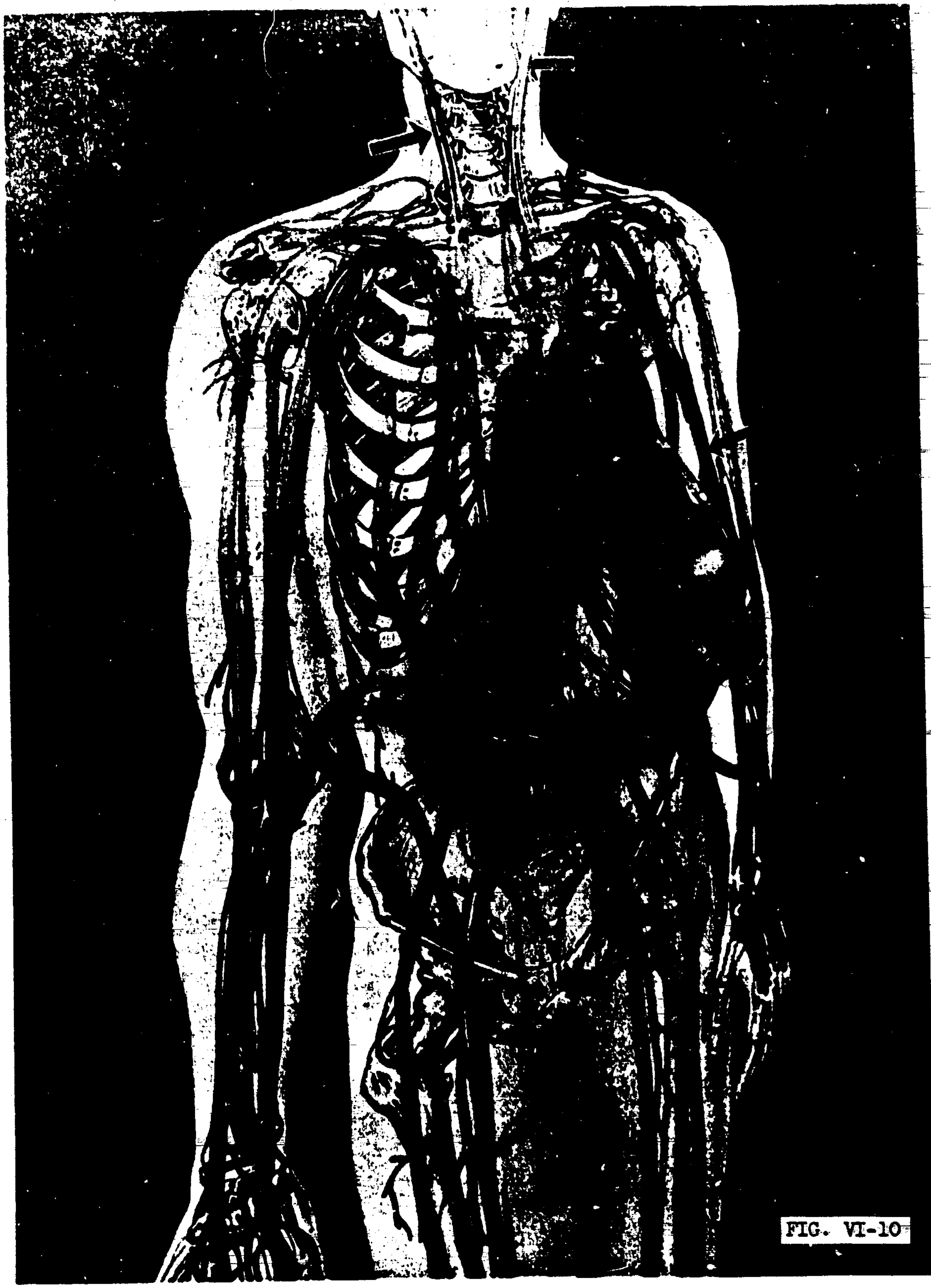
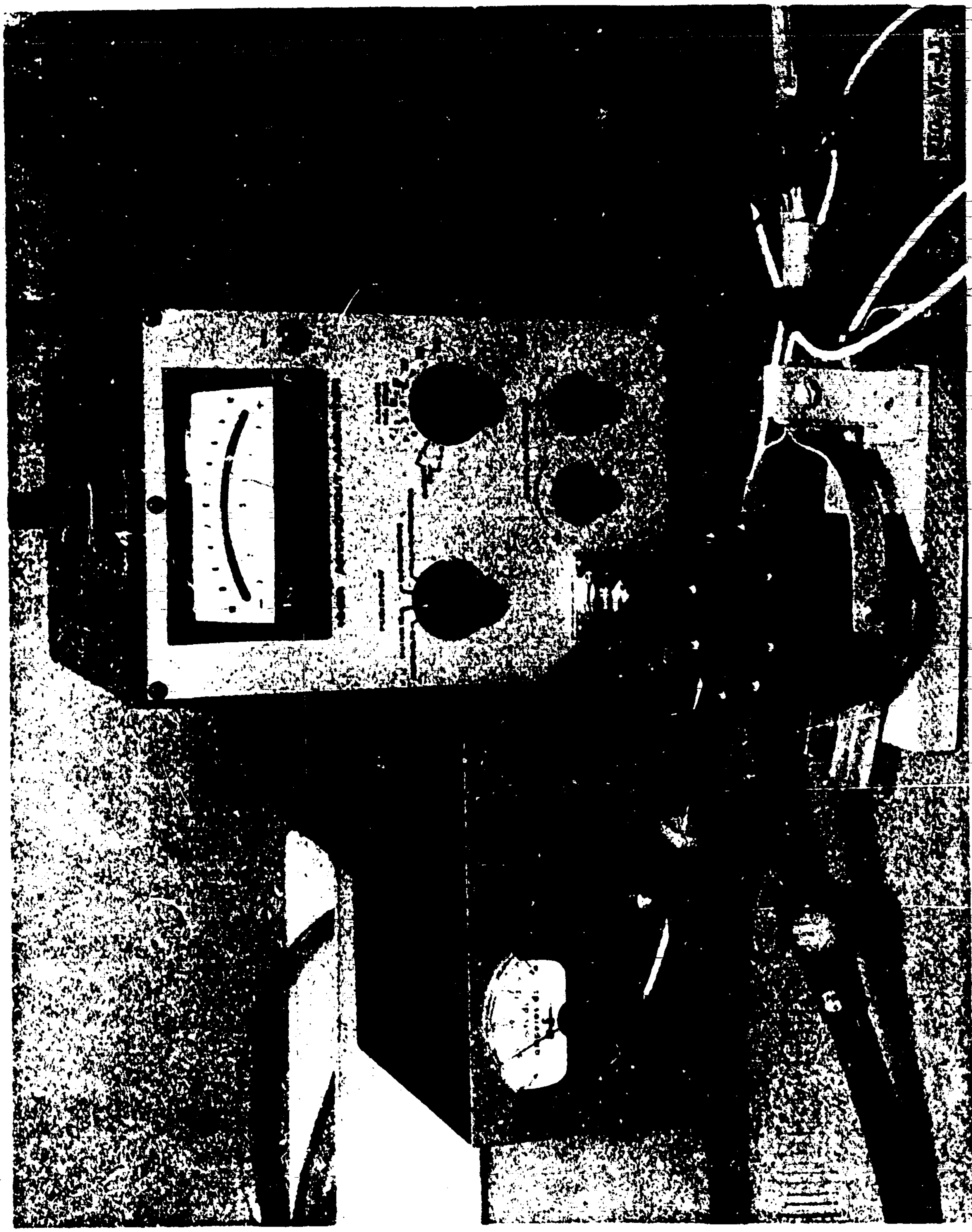


FIG. VI-10



is simple: we see little practical utility at this time in the detailed analysis of blood flow through selected portions of circulation. Strange as it may seem the literature contains very few attempts to construct a model of overall circulation and these are cited here. Data concerning the values of the system parameters are scarce. Sufficient information now exists to determine how cardiovascular models should be constructed but what is lacking are data on flows, impedances and compliances under conditions of full and partial weightlessness. Subsequent phases of this effort will be concentrated heavily on animal experimentation in an effort to determine if indeed underloading of the baroceptors and their subsequent reloading after a number of months does lead to transient myocardial weakness.

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A SERVOMECHANISM TO CONTROL THE OUTPUT OF AN ARTIFICIAL VENTRICLE

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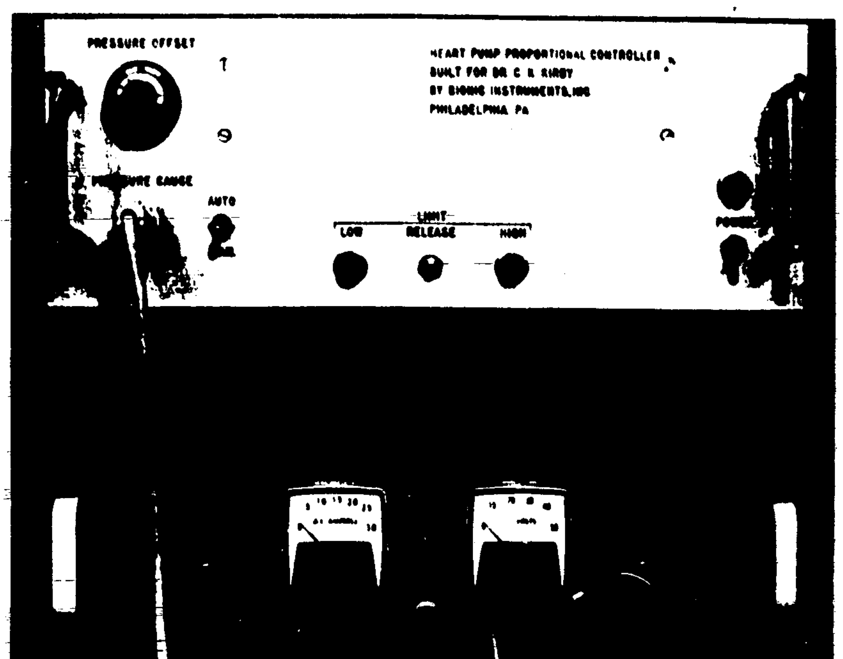
At present it appears important to be able to vary the output of an artificial heart to meet the varying circulatory needs of an experimental animal. The role of venous pressure has been recognized as an important factor in the control of cardiac output since the pioneer work of Starling (1). In congestive heart failure (2), ablation of nervous control as in complete heart block (3), and in denervated hearts (4), the importance of venous pressure has been demonstrated but the physiologic mechanisms involved have not been fully clarified.

Venous pressure has been utilized to control the flow rate of a heart lung machine (5), Sirak, Ellison and Zollinger found that venous pressure was a reliable aid in controlling flow in left heart bypass procedures (6). Saxton and Andrews noted the importance of venous pressure when non-occlusive centrifugal pumps were utilized for total heart replacement (7). Artificial hearts in which cardiac output is adjusted by variable filling proportional to venous pressure are another example in which venous pressure is of great importance in cardiac output control (8).

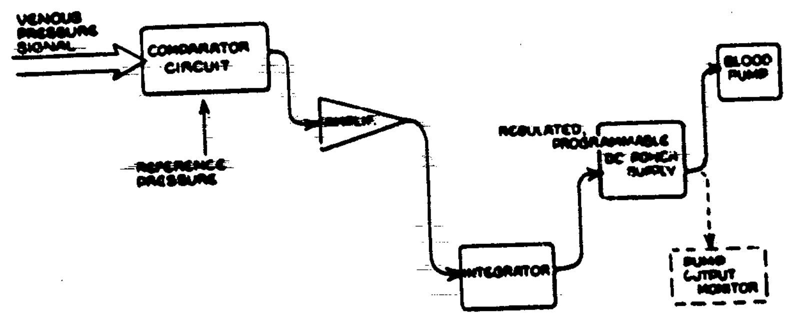
This report describes a servomechanism designed to control cardiac output by monitoring the venous pressure and adjusting cardiac output appropriately. The change in cardiac rate is proportional to the integral of venous pressure change from a predetermined value.

MATERIALS AND METHODS

The apparatus (Figure 1) consists of a strain gauge for measuring venous pressure, a servomechanism, and a regulated DC power supply with remote programming. The output of this power supply operates an artificial ventricle.

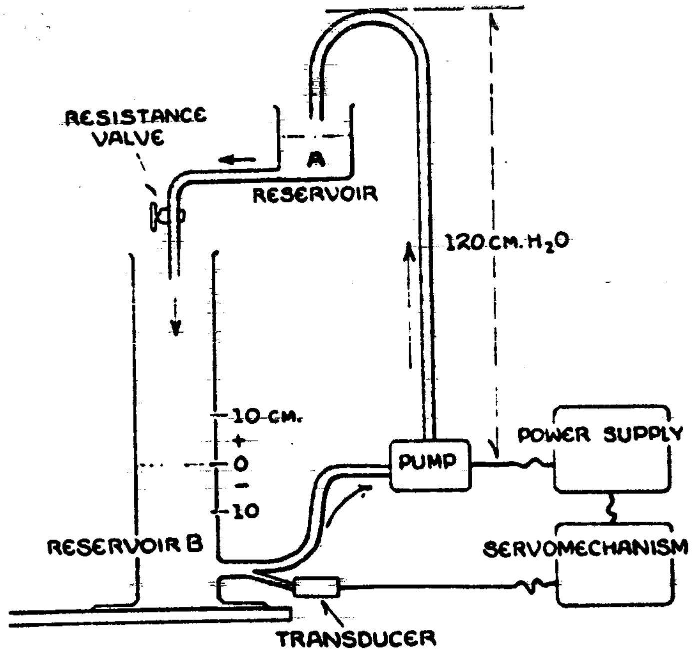


Servomechanism Operation



A block diagram of the servomechanism is shown in Figure 2. The venous pressure signal from a Statham pressure transducer (P23DC) is offset in the servomechanism by another voltage whose value is the "reference pressure" (Figure 2). Thus, when the venous pressure differs from the preset reference pressure, an error signal is generated. This voltage is fed into a DC amplifier (Brown 356413) whose output drives a 2 phase motor (Brown 362479-1). This motor turns a potentiometer which is connected to the "remote programming" terminals of a DC power supply (NJE Model TR36-2). Since the movement of the potentiometer is determined by the product of time and voltage to the motor, this has the effect of integrating the venous pressure and changing the pump voltage as a function of this integral.

The experimental set up used to evaluate the apparatus is shown in Figure 3. The pump used has been described previously (9). Briefly, it is a diaphragm pump of the piston type, powered by a DC motor and having a positive displacement. The pump output is proportional to the motor voltage. The output of the pump rises through a height of 120 cm. H_2O and empties into reservoir "A" (Figure 3). The flow from reservoir "A" to "B" is controlled by a valve, which may be used to vary the lumen of the outflow tubing. When the lumen was decreased in size, it was assumed, in this mock circulation set up, that the "peripheral resistance" was increased. The changes in resistance indicated later are produced by simply turning the knob.



To begin an experiment, the desired venous pressure (usually 0 cm. H_2O) was set on the "reference pressure" dial. The resistance valve (Figure 3) was opened to some arbitrary point, and the pump was started. It was considered that equilibrium was established when the level in reservoir "B" was constant.

In the first experiment the performance of the servo was tested by making sudden changes in the "peripheral resistance" (and, hence, venous return) and recording the consequent effects on venous pressure and pump voltage (heart output).

In the second experiment, a sudden change in the venous pressure was ~~made but the peripheral resistance was~~ held constant. The time required for the servomechanism to equilibrate following this change was measured at various flow rates and various magnitudes of venous pressure change. These changes were effected by pouring various volumes of fluid directly into reservoir "B" through a funnel

RESULTS

After allowing the system to come to equilibrium, the "peripheral resistance" was increased at the time indicated by the arrow in Figure 4. This resulted in an immediate decrease in venous pressure and was followed in about 2.5 seconds by a corresponding decrease in pump output. The pump output soon adjusted to the new flow rate into reservoir "B" and the venous pressure returned to the preset valve of 0 cm. H_2O.

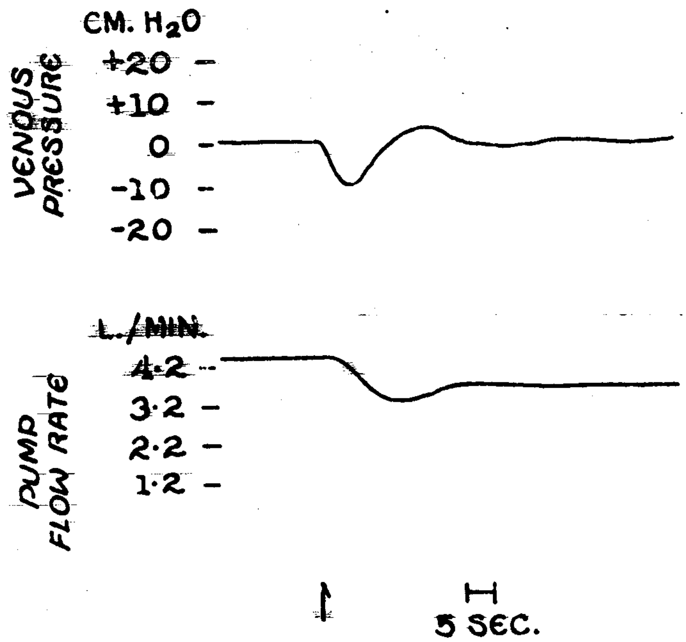
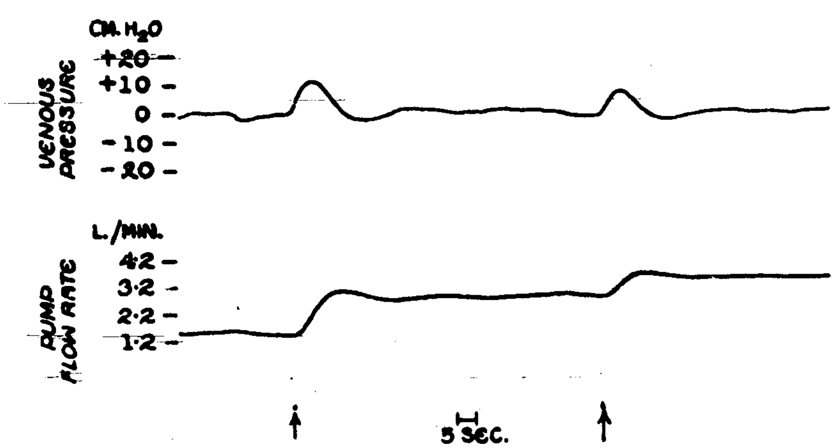


Figure 5 shows the result of 2 successive instances in which "peripheral resistance" was decreased by opening the valve. In each case, the venous pressure rose in response to an increase in flow into reservoir "B" and was promptly returned to the preset value by an appropriate increase in the pump flow rate.



The time required for equilibration varied between 23 and 37 seconds following venous pressure changes of 8 to 24 cm. H_2O. The number of observations was not large but no correlation between the time interval and the magnitude of pressure change or the various flow rates was apparent.

It is important to note that in this latter experiment, in which venous pressure was changed without changing "peripheral resistance", the pump flow rate returned to its previous value since no permanent change in venous return was made. However, in the first experiment (Figure 5) which did involve a permanent change in "peripheral resistance", the flow rate adjusted to a higher value to correspond to an increased venous return.

DISCUSSION

The use of venous pressure as a method of control of pump output allows

1) Maintenance of venous pressure within physiologic limits at all times thus preventing high venous pressure and subsequent pulmonary or peripheral edema, and preventing low venous pressure with consequent total collapse of the great veins.

2) A method of output control believed to be not unlike that seen in certain clinical situations.

3) The use of a small, reliable, pressure transducer as opposed to more complex blood flow or oxygen tension transducers.

The concept of operation of the apparatus described in which pump output is proportional to the integral of venous pressure differs from that of the Starling concept in that the venous pressure in this setup always returns to a single, preset "ideal" value as pump output changes. In the Starling concept, however, an increase in pump output is seen with an increase in venous pressure. The use of an integrating circuit adds electrical stability to the system in that no pump response is seen following such transient disturbances as venous valve opening and closure.

The ultimate use of this servomechanism for total heart replacement is where two such mechanisms are utilized, one to control right heart output and one to control left heart output. Such a system based on venous pressure regulation will function only if the circulating blood volume is relatively constant. It has become evident that circulating blood volume is a function of the blood flow rate. Gianelli, Robinson, Best and Kirby (10) have studied blood volume of animals on total cardiopulmonary bypass. Venous pressure varied from 0 to 10 cm. H_2O during the experiments. It was found that each animal's blood volume was a function of the perfusion rate. Higher flow rates were associated with greater blood volumes. A similar conclusion was reached by Fries, Broider, Hufnagel and Rose (11) who studied the effects of varying the output of a mechanical left ventricle on the circulation of the dog. These workers made no attempt to keep venous pressure constant.

In the intact animal, compensation for the required change is in blood circulating volume is accomplished by the large amount of blood stored in the pulmonary circulation and more complete systolic emptying of the ventricles (12). In the animal with an artificial heart of the positive displacement pump, one of these reservoirs is removed - that of more complete systolic emptying. A servomechanism which maintains a constant venous pressure will prevent further pooling of blood in the venous system during exercise and thus reduce the need for artificial blood reservoirs in conjunction with the artificial heart.

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VII. FUTURE DIRECTIONS OF THE CYBORG CONCEPT

A. Introduction

The NASw-512 Contract is a biological design study of man, particularly in alien or extra-terrestrial environments. It concerns itself with the systems requirements for the optimum life support, man monitoring-control, and spacecraft configuration design which will insure his safe and continued contribution to extra-terrestrial and space explorations. By thorough study of man's systems and subsystems when subjected to the simulated and actual conditions of extra-terrestrial environments, we will be able to make significant progress toward the better understanding of man as a space voyager.

In long-term space flights, the physiologic well-being of the pilot is of primary concern to the earth-bound medical monitors. While on such flights, the pilot/astronaut must be protected not only from all of the known hazards of space environment, but must in addition receive protection from those which are suspected to be of a debilitating nature. By the same token, the conquest of space by man must not be delayed by hyperprotective measures adopted through an overcautious approach to the unknown which require elaborate and unnecessarily redundant system designs. Only by a complete understanding of man's psychophysiological reactions to these hazards can we be permitted to let such flights take place, and be in a position to predict with any degree of reliability the probable success of a given flight.

As this report indicates, only selected areas merit detailed experimental efforts in the Phase II portion of the CYBORG Program. These are mathematical models (Biocybernetics), Sensory Deprivation, and Mineral Dynamics.

B. Biocybernetics

The ability to determine the performance of several aspects of the human organism while it is subjected to the stresses of space flight, without risking an astronaut's life, can be accomplished with a large measure of success by terrestrial simulation. Careful analysis of many aspects of human functions has shown that in many cases even the seemingly most complex systems can be reduced to mathematical relationships. By computer simulation and mathematical models of these systems we can develop an actual physical dynamic analog of the system under consideration. By subjecting these analogs to the environmental stresses of a space flight in terrestrial simulation laboratories we may be better able to gather a thorough understanding of the system dynamics involved and generate the design requirements for this aspect of manned space flight.

Phase I of the CYBORG Study has been concerned with the basic problem of conceptualizing and defining specific system components of man and the functioning of these components in an extra-terrestrial environment.

As part of CYBORG, considerable effort has been devoted to the synthesis of a non-linear mathematical model of the human cardiovascular system designed to reproduce the salient features of its functioning under several environmental conditions and, possibly, under certain types of psychological inputs. In the continuation of the CYBORG concept in Phase II, efforts will continue to be devoted to the development and exploration of a cardiovascular system model and will be extended to other human systems and subsystems. It is recognized that the experimental verification of this analytic model in all detail cannot be undertaken without access to a gravitation-free environment. It is possible, however, to perform significant experimental work in animals which have been subjected to surgery in which their carotid sinuses and other baroceptors have been denervated. These animals can be thus regarded as "pseudoweightless" from the cardiovascular viewpoint, and hence can be used in studies designed to evaluate the response of the cardiovascular system to certain standard inputs such as would be encountered in rapid re-entry from a deep space mission.

Since one ultimate objective of this program is the design of sensing and processing systems, it must be emphasized that ultimately some aspects of this work must be performed under actual operational conditions in man. It is not possible or desirable at this time, however, to do more than point out the necessity for this ultimate test. Additional understanding of human cardiovascular dynamics can be expected to improve the precision with which we can specify more nearly optimum sensor-processing systems. For example, blood flow or vascular current is an important but difficult to measure physiologic parameter. It is conceivable, as shown by F. Cope, that blood flow can be determined indirectly from data on blood pressure and blood vessel compliance.

Relationships such as the one indicated above have been investigated as part of Phase I and should certainly be further studied in this proposed program. The availability of molecular integrated circuit techniques makes it entirely conceivable that once a set of rational requirements has been generated, small sensor-processer units can be designed which will handle the data in a manner which will permit the display of more meaningful cardiovascular variables. Even in those cases where it is not feasible or desirable to incorporate the data processing elements in the sensor packages themselves, the processing methods can still be incorporated in suitable computing devices for remote handling and display. After this objective is accomplished, studies will be undertaken to explore the utility of preparing analog packages of the human vascular system. Such packages, once developed, would prove useful in both terrestrial experimentation and in the preliminary exploration of extra-terrestrial environment.

C. Sensory Deprivation

This area has been included in the CYBORG Study because many reported effects of sensory deprivation constitute a serious modification of normal functioning, and there are grounds for supposing that the space capsule constitutes a restricted environment which provides significantly less sensory stimulation than that to which humans are usually accustomed. A major contingency which must be guarded against on any extended space mission is the induction of hypodynamic conditions as a result of the failure of any component. For example, loss of power could result in the cutting of communications with earth station. In order to maximize the probability of survival, it is essential that design requirements be specified and devices be incorporated which will maintain the sensory environment at a high dynamic level.

The major purpose of the proposed study is the identification and evaluation of the means by which man can be prepared to cope successfully with the many psychological stresses which may affect him during long-term space missions. The need for this work arises because man is basically a biological organism designed to operate within the parameters defined by the earth environment. Despite a remarkable degree of overdesign, there are many areas in which man's capabilities fall short of requirements posed by such missions.

On the basis of the present analysis, time-structuring events such as programs of moving displays, sound, and recorded material of interest to the crew seems to merit investigation. Other activities such as problem-solving requirements and sequential tests may be promising. The design requirements of such devices should receive the highest priority. By presenting to the pilot changing patterns of sensory inputs, we may be able to control his possible lapse into a state of sensory deprivation and prevent its attendant incapacitating effects from ever occurring. In addition, it is felt essential that means be formulated which will have the capacity to monitor the status of the CNS. Such a device would be able to determine the level of CNS reactivity to a marginal signal input and determine whether quite unconsciously the pilot is gradually losing control of his conscious mental processes.

D. Mineral Dynamics

On each of the three United States manned orbital flights, collected in- and post-flight urine specimens showed significantly elevated levels of excreted calcium. This is a phenomenon which has been frequently observed in the past in cases of hospital patients subjected to extended periods of immobilization, in sensory deprivation studies, certain stress situations, and in simulated weightlessness experiments involving water immersion. It remains to be determined, however, whether this increase reflects potentially serious drainage of calcium from the skeletal system. In order to monitor and appraise the significance of alterations in calcium output, it is necessary that a detection system be devised which will permit the tracing of the mineral through the several metabolic compartments.

It can be unequivocally stated that no method is known today for determining calcium movement other than those methods involving some type of tracer. It is to be emphasized that passive neutron activation methods are capable only of "static estimates of calcium." The elucidation of the dynamics of the mineral requires the use of distinguishable but chemically identical atomic species. Therefore, a suitable system for the detection of calcium dynamics must involve:

1. The use of a tracer,
2. A suitable sensor, and
3. The application of correct data processing techniques to the information collected.

In the course of this proposed program, we shall continue the investigation of calcium dynamics in man and animals from the viewpoint of the changes which occur as a result of immobilization and/or psychological stress and establish the requirements for a detection system to determine and display changes and predict trends in the pilot's calcium dynamics.

The CYBORG program is expected to be a long range program of study and experimental efforts. The experimental phases are intended to develop both mathematical and physical dynamic models of important human systems. These will include the cardiovascular, endocrine, gastrointestinal, cutaneous, and pulmonary systems. The physical models will be verified by actual laboratory experiments and relating mathematical formulae will be developed to describe interaction of the systems. These models will be simulated on the UAC computer facility and dynamically tested, ultimately, in space environmental extremes. Firm design requirements will be established for an optimized physiologic monitoring system as well as for the design requirements for a life support environmental control system. Such systems will be integrated to provide a total man-machine complex with man in the control loop as the forcing function. Space capsule design requirements will be delineated, as well as a result of sensory deprivation experiments and man-augmentation mechanism design constraints.

These design requirement "groups" will be developed in such a way that a relatively simple modification scheme will allow the requirements to change and up-date the state of the art as time progresses. This will prevent the necessity of having to fund an entirely new program every few years to redevelop design requirements as the changing state of the art makes existing requirements groups obsolescent.

Out of the CYBORG program we will be able to understand considerably more about man, his systems and his subsystems. Methods for augmenting and extending his limitations, which will be compatible with the state of the art and the applicability of man in a space mission will be derived from CYBORG in an effort to obtain the maximum integration of man into a man-machine complex.

Hopefully, we will evolve a model of the central nervous system during this period. This is an ambitious task, but must be earnestly assaulted if such a worthy undertaking is to ever be completed.

A significant number of experiments will be performed on animals and man throughout this program to verify the modeling concepts which have evolved from the CYBORG theory. In this way, CYBORG will accomplish its mission by providing a better understanding of the biological design of man and relating the impact of this understanding to compatible hardware systems.